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ELECTROCARDIOGRAPHIC CHANGES IN
CHILDREN TREATED WITH ALPRASIDONE:
A PROSPECTIVE STUDY AND REVIEW

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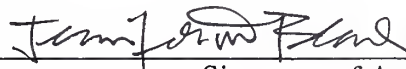
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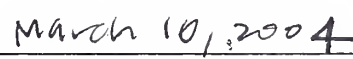


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ELECTROCARDIOGRAPHIC CHANGES IN CHILDREN TREATED WITH
ZIPRASIDONE: A PROSPECTIVE STUDY AND REVIEW

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Jennifer Melissa Blair

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ELECTROCARDIOGRAPHIC CHANGES IN CHILDREN TREATED WITH ZIPRASIDONE: A PROSPECTIVE STUDY AND REVIEW

Jennifer Blair, Lawrence Scahill, Matthew State, and Andrés Martin. Yale Child Study Center, New Haven, CT.

This study assessed the electrocardiographic (ECG) safety profile of low-dose ziprasidone (Geodon) (≤ 60 mg/day) among pediatric outpatients treated for up to six months, and compared electrocardiographic intervals generated through manual versus automatic methods. Literature on the electrocardiographic safety in children of three major classes of psychoactive medications, as well as on the vicissitudes of the electrocardiographic QTc interval as a marker for clinical risk, is also reviewed, and safety guidelines are presented. The study was a prospective, open-label trial involving 20 subjects with a mean age of 13.2 ± 3.0 years. Subjects received a mean ziprasidone dosage of 30 ± 13 mg/day and were followed for 4.6 ± 2.0 months, receiving a median of 9 ECGs each. There were statistically significant changes from baseline to peak values in heart rate, PR and QTc intervals, but not in QRS complex width. The mean QTc interval increase from baseline to peak was 28 ± 26 milliseconds (msec), and not related to dosage ($r = 0.16$, $p = 0.07$). The peak QTc of three subjects reached or exceeded 450 msec. One subject experienced a 114-msec prolongation. There was poor agreement ($\kappa = 0.25$) between automated and manual identification of prolonged QTc intervals (≥ 440 msec). In low doses, ziprasidone causes a clinically significant increase in the QTc interval in children and adolescents. Periodic ECG monitoring is warranted when prescribing ziprasidone to children, particularly at higher doses. Automated measurements of the QTc interval should not be relied upon to evaluate prolongation.

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Andrés Martin, who gracefully melds persistence, patience and goodwill, has over the course of a year gone from benevolent clerkship boss to multi-project collaborator to valued friend. *Oy, the naches!* Simply: thank you. Pfizer Incorporated provided study drug and financial support for electrocardiograms. Drs. Matthew State, Lawrence Scahill, and Lawrence Cohen provided timely and valuable critiques. I would also like to thank Blake Taggart, whose initial investigations guided the beginnings of my literature search. My sister, Elisabeth Catherine Blair, supported this project just by being herself. I wish that I had more of her.

I sing the body electric...

Walt Whitman

Leaves of Grass

MANUSCRIPT NOTE

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PREFACE

Psychiatry, while primarily concerned with mental illness, is also properly involved with the care of other organ systems. Many mental illnesses can wreak havoc on the body, whether because of inherent physiologic associations with the primary disorder, behavioral changes leading to self-abuse or neglect, or medications used to treat their manifestations.

Ties between the mind and the cardiovascular system are increasingly being described, as our understanding of the nervous system and its effects on heart rate and other parameters grows. Immediate daily concerns for the practicing psychiatrist arise because many of the drugs in his armamentarium exert direct and potentially deleterious effects on the heart – effects that can be visualized by, among other means, the electrocardiogram (ECG). Prolongation of the corrected QT interval is considered the most worrisome manifestation of a psychoactive medication's effect on the ECG, because such prolongation may be associated with lethal arrhythmia and sudden death. Children are not immune from these effects, which have been noted most conspicuously in this population in association with the tricyclic antidepressants. The precise mechanism for all ECG changes is not fully understood, but it is known that blockade of sodium channels is often the culprit in cases of QTc prolongation. In turn, QTc prolongation is associated with torsades de pointes, an arrhythmia which may be fatal. Because of the potential lethality of the drugs in question, it is important to be able to monitor the patient for warning signs.

It is then that the accuracy of the ECG becomes a vital issue. The QTc interval, while at present our best means of predicting dangerous arrhythmias, is in many ways a

problematic parameter. It is corrected for heart rate, but is inaccurate at extremely slow or fast rates. Many nonpathologic factors affect its duration, such as gender, age, time of day, and postprandial state. The way in which the QTc is measured varies, along with accuracy. Even the cutoff time for dangerous prolongation is not universally agreed upon. In children, the problem is even less clear-cut. Children were seldom included in early studies which devised QT correction formulas, so it is not clear how well the most popular formulas apply. Experience with pediatric patients and many psychiatric medications is typically less extensive than with adults, with a resulting lower power to predict and study adverse events.

This thesis contains three main parts. A literature-based discussion of the intricacies of measurement and interpretation of the QTc parameter is followed by a review of the literature regarding the three classes of psychotropic medications with the greatest potential to cause QTc prolongation, specifically as they have been studied in pediatric patients. These are followed by a report of a prospective, open-label study of the effect upon QTc of a new atypical antipsychotic medication in twenty children and adolescents, as well as of the comparative reliability of two methods of measuring that interval.

It is hoped that this thesis will shed some light on these complex issues and provide some guidance to child psychiatrists who may be unfamiliar with the finer points of the cardiac effects of the drugs they rely upon, and of the limitations of the measurement methods used to detect those effects.

INTRODUCTION AND BACKGROUND

Some of the more serious complications of pharmacologic therapy in psychiatry are cardiac, and range from benign changes in heart rate and blood pressure to heart block, potentially lethal arrhythmias, and sudden death. Many of these changes, whether silent or symptomatic, can be detected by electrocardiogram (ECG) – prolongation of the QTc being a prominent example. There are often few data regarding the safety of psychiatric medications in children and adolescents, so the use of these drugs requires heightened caution. These concerns have gained clinical immediacy in the wake of: a) reports of sudden deaths associated with the tricyclic antidepressant desipramine (1), b) concerns over the potential cardiotoxicity of combining stimulants and alpha agonists in the treatment of attention deficit-hyperactivity disorder (2), and c) widespread use in children and adolescents of antipsychotic drugs – both traditional and atypical – known to have direct cardiac effects. After reviewing key points about the QTc interval, this section reviews the most important psychiatric medications that cause ECG changes in children, with a particular focus on prolongation of the QTc interval, and proposes recommendations for screening and monitoring during treatment.

SEARCH STRATEGY FOR LITERATURE REVIEW

MEDLINE (1966-2003) and EMBASE (1980-2003) searches were conducted for each of the drugs discussed below, with the following strategy: the drug's generic name was combined with each of the terms *electrocardiogram*, *overdose*, *sudden death*, *arrhythmia*, and *torsades de pointes*. These searches were then repeated with the additional term *child*. Relevant articles were identified from search results, and

additional articles were identified from bibliographies. Except where otherwise noted, the search was last updated in September, 2003.

THE QTc INTERVAL: CARDIAC ELECTROPHYSIOLOGY AND CLINICAL MEASUREMENT

The QT interval of the ECG is the measured distance between the beginning of the QRS complex and the end of the T wave; it comprises depolarization and repolarization of the ventricles, and reflects the many processes that go to make up those events. Depolarization in myocytes is mediated by influx of sodium and calcium, while repolarization is mediated through outflow of potassium; anything that alters the balance of ion flux in favor of more positive intracellular ions can lead to prolongation of the QT (3). The rapidly-activating potassium rectifier channel, IKr, which is encoded by the human ether-a-go-go gene (HERG), is crucial to repolarization; mutations in this gene underlie some forms of congenital long QT syndrome (LQTS), while inhibition of the channel by medications may explain their QT-prolonging effects (4, 5). Several other genes encoding parts of the membrane potassium (IKs) and sodium channel proteins have also been identified in LQTS (6-8).

The QT interval shortens with increasing heart rate, and is usually corrected to yield the QTc. This parameter, used in research for several decades, is considered the best marker available for predicting lethal arrhythmias. QT dispersion, or the difference in QT intervals between leads on the same ECG, is being studied, but has not superseded the QTc (9-11). Torsades de pointes (TP), first described in 1966 (12), is an often lethal arrhythmia that is almost always preceded by a lengthened QTc interval, and is often associated with the sudden deaths of patients on QTc-prolonging medications and those with congenital LQTS. It is hypothesized to follow early afterdepolarizations –

spontaneous depolarizations occurring in nonpacemaker cells – made possible by delayed repolarization (13). Though the exact value is not completely clear, many workers agree that a QTc > 500 msec leads to an elevated risk of this arrhythmia, though a direct relationship between QTc prolongation and risk of arrhythmia is not necessarily present in drug-induced cases (13) (it has been established in congenital LQTS (14)). Some drugs cause marked prolongations without serious sequelae – amiodarone, for example, though it may lengthen the QTc to greater than 600 msec, is rarely associated with TP (15) – while others are associated with TP at a shorter QTc (16).

The QTc is an imperfect parameter, however. Even for the simple correction for heart rate, many formulae have been proposed, but none is universally applicable. The most popular, the Bazett formula (17), divides the QT by the square root of the R-R interval. Yet this formula derives from a study that examined only 39 adult subjects, and is known to be nonlinear at fast heart rates (11). Despite these shortcomings, the formula is used widely, which simplifies comparisons between different studies. Other formulas are available, including some derived from studies which included children (10), but these are not in general use. Some workers argue that the QT/RR relationship exhibits so much inter-individual variability that a unique formula should be established for every subject (18), while others propose not correcting the QT, but simply reporting the heart rate at which it was recorded (19). These suggestions could help improve accuracy and standardize research studies, but at a prohibitive cost of convenience to the clinician. On the other hand, Bednar et al (10) point out that in at least two studies using the QTc interval (20, 21), several different correction formulas yielded comparable results.

Apart from the method of correction for heart rate, other inconsistencies plague studies that use the QTc interval. Measuring the QT itself can be difficult when the presence of a U wave makes it unclear where the end of the T-wave lies (14, 15, 22), and results are difficult to compare across studies when different leads are used from one study to another (different leads on a 12-lead ECG show differing values of QTc, though this difference is most pronounced in subjects with myocardial infarction (23)), or when some studies use manual measurements while others rely on machines. Studies of QTc intervals derived from Holter monitoring should not be compared with studies that used standard 12-lead ECGs, as Holter measurements tend to be significantly different from 12-leads (24). The QTc relationship changes over several minutes while heart rate is changing, such that measurements taken during a change in heart rate show a falsely elevated QTc (22).

Many physiologic factors influence the QTc, such that to speak of a patient's QTc is rather like speaking of his glucose level – a single value is of limited utility. QTc itself varies by gender, though not before puberty (14, 25). A diurnal variation has been demonstrated in adults (26, 27). Psychopathology itself may influence the interval, through changes in autonomic tone that can alter parasympathetic input to the heart (28). Many other confounders, including comorbidities and electrolyte disturbances, have been identified (10). Studies do not necessarily take these factors into account, and it can be unclear whether changes in the QTc can be ascribed to the intervention being studied, a confounder, or just physiologic variation.

With respect to diurnal variation in particular, drug studies have sometimes downplayed the significance of drug-induced QTc prolongation by pointing out the large

diurnal variations in QTc that have been documented in adults. A study of 21 healthy men who had undergone Holter monitoring found an average daily variation of 95 ± 20 msec (29). A retrospective study of 84 men and women participating in 11 unrelated pharmaceutical studies found variations between 7.0% below and 7.1% above an 8 A.M. baseline QTc (only unmedicated ECGs were examined; also, this study did not report using Holter monitor data) (26). Another study of 20 healthy men found that a manual measure of QTc varied over 24 hours of Holter monitoring by a mean of 76 ± 19 msec (range, 35 to 108 msec) (27). The authors of a study of the drug sertindole, which was removed from the market for QTc prolongation, argued that the 19.7-msec increase they found was not clinically significant because it fell within normal diurnal variation (30). A rejoinder to this argument, however, might be that since people have different baselines and differing rates of metabolism of medications, and because studies are so unstandardized that a typical patient will not necessarily be comparable to study subjects, any tendency to cause QTc prolongation by a drug is potentially hazardous. This appears to be the FDA's position, which has required warning labels for drugs that prolong the QTc in this range. Caution would appear to be doubly warranted in children for the reason that data about possible diurnal QTc variation in healthy pediatric patients are lacking. (No studies could be found in the literature as of this writing.) Because the underlying causes of QTc variability throughout the day are poorly understood, it is difficult to speculate as to variability in children in the absence of actual data, so this phenomenon should not be resorted to as a reason to be unconcerned by increases in children.

Clinicians often rely upon automated, machined-generated measurements of the QTc as a quick check on whether it is prolonged. However, manual measurement is considered much more accurate (11, 22, 31, 32). There are several reasons for this: the T-U wave transition can be ambiguous and may be misjudged by a computer; the QT may vary from lead to lead; and technical factors such as paper speed may affect sensitivity (32). Malik and Camm (22) discuss these phenomena in detail and provide dramatic examples of automated measurement inaccuracy; in two cases, the computer overestimated QTc by over 100 msec in the presence of physiologic U waves. Anderson et al (11) provide separate guidelines for large versus small U waves, recommending that the former be included and the latter excluded in QT measurement. A study examining a family with congenital LQTS compared automated measurements to those obtained with a manual method that involved measuring all twelve leads, and found that six of twenty-two subjects would have been misclassified by relying on the computer's diagnostic interpretation. Although the computer's QTc measurements agreed well with the manual measurements in this study, the authors strongly recommended manual measurement of the QTc, partly because the ECGs of the family they studied displayed unusually clear-cut T waves that may have aided computer recognition (31).

Guidelines for measuring the QTc in pharmaceutical studies have been put forward by a group of experts on congenital LQTS, which include recommendations to measure the interval manually during peak plasma drug concentration, and to average the results of 3 to 5 heartbeats (11). Once a measurement is available, there are discrepancies amongst studies regarding whether QTc changes are reported as maximum or mean changes from the subject's personal baseline (usually only one point, which some studies

do not check at all), or as a value compared to an arbitrary “abnormal” cutoff. This cutoff varies greatly in the literature. An extensive review of many reported instances of TP by Bednar et al (10) concluded that there was substantially greater risk of this arrhythmia only above a QTc of 500 msec. A review of the effects of psychotropic medications in children (33) used 440 msec as a cutoff for concern, as have a number of other workers (24, 26, 27, 34). A study of 158 children aged 1-15 years yielded suggested values of under 440 msec as normal, 440-460 as borderline, and 460 as prolonged in this age group (14). Several studies of subjects with congenital LQTS have provided more insight into values of concern in that population (31, 35, 36). In any case, it is unclear which method of comparison – change from personal baseline or difference with respect to an abnormal value – is the more predictive of cardiac adverse events. The Committee for Proprietary Medicinal Products (37) states that an individual QTc prolongation of 60 msec or more put subjects at risk of arrhythmias. The authors of a study demonstrating diurnal variation in adults reviewed the literature and suggested that drug-related prolongation be considered clinically significant only if more than 5% of subjects had QTc intervals over 500 msec, or if any individual had a QTc prolongation by > 75 msec over baseline (27). It should be borne in mind that many studies of QTc prolongation and cardiac risk examined adults with heart disease, and this may not be generalizable to healthy children receiving psychotropic medications.

There are other problems with interpreting QTc study results. Dosing of medications and their schedules varies from study to study, though this problem is not unique to QTc research. In real life, patients do not always take only one drug at a time; interactions are crucial to consider, and many adverse-event reports describe patients who

were taking more than one medication. The sensitivity and specificity of QTc prolongation for arrhythmia are unknown (13). For these reasons, it is as yet impossible to use the QTc to accurately predict risk of TP or sudden death for individual patients or with specific agents (38). A fuller discussion of these issues can be found in Bednar et al (10), which includes a table of proposed QTc correction formulas, and Labellarte et al (39), which is specific to pediatrics.

In summary, owing to a lack of data in even adult studies, there are substantial gaps in our knowledge of the phenomenology of QTc prolongation by psychotropic medications. However, the fact remains that prolongation is known to be associated with TP and sudden death, particularly prolongation > 500 msec. Diurnal variation has not been studied in the pediatric population, and prolongations in children should not be discounted for that reason. It would seem that, until better measures or measurement techniques are developed, the clinician would do well to exercise caution in the face of a prolonged QTc when using psychoactive medications in children. Details on worrisome ECG changes and recommendations for monitoring will be provided below.

EFFECTS OF PSYCHOTROPIC DRUGS ON THE QTc INTERVAL IN PEDIATRIC PATIENTS

Several groups of psychiatric medications in children are of especial interest with regards to prolongation of the QTc interval. These are the antipsychotics, both atypical and typical, the alpha-agonists, and the tricyclic antidepressants.

Antipsychotics: atypical agents

Risperidone (Risperdal) is an atypical antipsychotic approved in 1994 and used to treat bipolar disorder, conduct disorder, pervasive development disorder, psychotic and tic disorders. Reports of adverse cardiac events are few, and there appear to be none in

children apart from several episodes of QTc prolongation. A toddler being treated with therapeutic doses of risperidone for severe autism developed persistent QTc prolongation as well as tachycardia (40). A 7-year-old boy developed central nervous system abnormalities after only one therapeutic dose; the symptoms worsened after a second dose, and a QTc of 460 msec was noted (41). A sudden death occurred in a 34-year-old woman treated with therapeutic doses who developed a QTc interval of 480 msec (42); she was being treated concurrently with amantadine and haloperidol. Risperidone in overdose in adults has been reported to cause prolonged QRS and QTc (43, 44) as well as isolated sinus tachycardia (45, 46) and in some cases no ECG abnormalities (47). There have been very few reported cases of pediatric risperidone overdose. A 3-year-old boy following an accidental 4 mg ingestion was found to have extrapyramidal symptoms, but no ECG abnormalities (48). None of the pediatric poison-control cases reviewed by Catalano et al (49) mentioned QTc abnormalities, and in the case reported in that paper – a fifteen-year-old girl who ingested 110 mg – only sinus tachycardia was evident on ECG. However, in an accompanying review of adult overdose reports, three of seven adult patients developed QTc prolongation (49). Another review of 48 overdose cases found increased QTc in five patients (50). Evidently, QTc prolongation is a possibility in risperidone-treated patients of all ages, not only in overdose but also in therapeutic dosage in certain patients. However, it appears to be a rare event.

Olanzapine (Zyprexa), along with risperidone, is one of the most widely-researched atypical neuroleptics in pediatric psychiatry(51). Its influence on the QTc has been scrutinized in a number of studies and case reports. In Czekalla et al's (52) complex analysis of four studies of olanzapine, the ECG of 2700 patients (mean age 38 years,

ranging from 18 to 86) revealed average prolongation by 8.44 msec from baseline in one study subgroup, with shortening by 7.83 msec in another study's subgroup and no change in the remaining eight subgroups. Furthermore, the incidence of prolongation over 450 msec was no higher in treated groups than it was at baseline. The authors concluded that QTc prolongation contributing to fatal arrhythmias does not appear to be a concern in olanzapine-treated patients. A study of seven psychoactive medications and their effects on the HERG potassium channel found that olanzapine was the most selective of the seven for dopamine and serotonin receptor binding relative to HERG potassium channel affinity, suggesting it would have a lesser propensity to block the channel and lead to QTc prolongation (5). However, there has been a report of QTc prolongation, from 412 to 485 msec, in a 28-year-old woman receiving higher doses (40 mg/day) than most of the ones studied in the above reviews (20 mg/day) (53). PR prolongation and first-degree heart block have also been reported (54).

Overdose experience with olanzapine is modest but includes a number of pediatric cases. As reviewed in Catalano et al (55), lethargy and tachycardia are frequent and prominent symptoms, but not other electrocardiographic abnormalities. The pediatric presentation is dominated by these CNS abnormalities and is treated supportively. Several other cases have been reported without information about ECG intervals; CNS toxicity and tachycardia were prominent (56-58). Adult overdoses sometimes mimic opioid overdose, and have featured tachycardia and CNS toxicity, generally without QTc prolongation (59-63). At least two overdose deaths have been reported, as reviewed in Burns' (50) review of 21 overdose cases. Searches of the literature using the strategies described earlier reveal no reports of pediatric or adult sudden death, TP, or arrhythmia

associated with the use of olanzapine. A Canadian Adverse Drug Reaction report, however, named olanzapine as a suspect in three reports of fatal arrhythmia, one of which involved several coingestants, and one case of QT prolongation, which involved the coingestants quetiapine and valproate (64). On balance, it would appear that evidence for QTc prolongation by olanzapine is, at best, equivocal, and that the drug is safer than other antipsychotics in this regard, at least in relatively low doses.

Quetiapine (Seroquel), introduced in 1997, is an atypical antipsychotic similar to clozapine. A study in ten adolescents (65) found a small increase in heart rate; a common adverse effect was postural tachycardia. No subject's QTc rose above 500 msec, or by more than 60 msec from baseline; no information was provided on whether any subject's QTc exceeded 440 msec. Another open-label study of adolescents (51) found no changes in the PR interval, the QTc interval, or the QRS interval after eight weeks of quetiapine, though a small mean increase in heart rate and blood pressure were noted. These results are somewhat encouraging, but total only 25 subjects, all of whom are adolescents. There is still very little information on the effects of quetiapine in younger children, and no large-scale studies.

There are a few reports of pediatric quetiapine overdose. One case occurred in a 15-year-old girl (66), and another in an 11-year-old girl (67). The 15-year-old developed systemic symptoms which included tachycardia up to 188 bpm, while an ECG six hours post-ingestion found a QTc of 437 and a heart rate of 97. No cardiotoxicity was noted in the case of the 11-year-old. Burns reviewed adult overdoses and found QTc prolongation in only one of 216 cases (50). A case reviewed in Catalano (66) reported an increased QTc, after a ingestion of 9600 mg of quetiapine in a 19-year-old male. The QTc rose to

710 and resolved after a day (68). He, too, was tachycardic, an effect that is noted in the other reported overdoses. One adult death has been reported in association with an adverse reaction to quetiapine, but no details were available (69). No pediatric deaths after solely quetiapine ingestion, either in therapeutic or toxic doses, have been reported to date.

Ziprasidone (Geodon) is a relatively new atypical antipsychotic that is effective in the treatment of positive and negative symptoms of schizophrenia and schizoaffective disorder (70-72). It is a benzothiazol, chemically unrelated to phenothiazines or butyrophenones, and has a strong affinity for serotonin 5HT_{2A} and dopamine D2 receptors (73), and a lesser affinity for several other receptors (74). It is valued for its superior side effect profile, including a lesser tendency to cause weight gain (75). It has been under close scrutiny by the FDA before and since its approval in 2001 owing to its propensity to prolong the QTc interval more than many other atypicals. The mechanism of this prolongation is likely to involve blockade of the cardiac HERG potassium channel, although a study found that it was found to be more selective for two of its therapeutic receptors relative to HERG than were thioridazine, pimozide, and sertindole (5). A placebo-controlled study by the manufacturer found prolongation of 10 msec compared with placebo (76). Another study by the manufacturer, Study 054, compared the QTc prolongation by ziprasidone to that caused by other drugs, as well as to the patients' own baselines; this study did not include a placebo control. The group taking ziprasidone consisted of 25 men (mean age, 38.6 years, range 22-58 years) and 10 women (mean age 36.1 years, range 20-47 years) with baseline QTc < 450 msec (Bazett-corrected). 33 members of this group were eventually titrated to maximal doses of 160

mg/day (gender of two missing patients unspecified). With respect to patients' own changes from baseline, of those 33, the QTc increased by ≥ 30 msec in 21 subjects (64%), by ≥ 60 msec in 7 subjects (21%), and by ≥ 75 msec in one subject (3%) (patients with greater changes were also counted as falling into groups of lesser change)(77)^A. The mean absolute increase from baseline in QTc was 20.6 msec (5%). With respect to other drugs, the study found that ziprasidone prolonged the QTc interval 9 to 14 msec longer than did risperidone, olanzapine, haloperidol, and quetiapine, but 14 msec less than did thioridazine (76). An FDA reviewer concluded the effect was concentration-dependent (77). Intramuscular administration of ziprasidone was found to increase the QTc almost the same amount as haloperidol causes. The manufacturer also reported that sudden deaths had occurred in patients taking therapeutic doses, but that the number of deaths did not exceed that of other drugs (76). Keck et al (78) studied 131 adults with bipolar mania taking doses from 80-160 mg/day and found an 11-msec mean increase of the QTc over baseline. 66 patients assigned to placebo were also analyzed, but mean QTc values of the two groups are not reported. A review in 2001 found no overdose deaths, TP, or excess of sudden deaths (79). Searches of the literature using the strategies described earlier reveal no reports of sudden death or TP associated with the use of ziprasidone in either adults or children.

Only a few studies have examined the safety and efficacy of ziprasidone in pediatric subjects. A double-blind, placebo-controlled study of 28 pediatric patients with Tourette's syndrome treated with ziprasidone found no clinically significant changes in ECG parameters during treatment as compared with baseline (80). An open-label trial in

^A Page accessed March 2004.

8 adolescent boys found an increase in QTc of 17.3 ± 28.6 msec (81)^A. A study of the use of ziprasidone in 12 patients between the ages of 8 and 20 found no clinical cardiac effects; however, beyond a baseline pretreatment ECG, no ECG testing was performed (82). A chart review of thirteen children found a 19-msec prolongation in the one child for whom both baseline and follow-up ECG data were available (83).

Experience with overdose is also limited. In the case of a 17-month-old girl who ingested 400 mg, transient tachycardia to 240 bpm, developed with a QTc of 480 msec and BP of 121/60. The child recovered after an uneventful day of monitoring. The two other patients in the same series, who were adults, developed QTc prolongation to 459 msec (with cocaine and heroin coingestion) and 638 msec (with quetiapine coingestion; it fell to 486 msec after magnesium sulfate treatment) (84). One overdose with ziprasidone, bupropion, and benzodiazepines was taken by a 17-year-old boy who developed QTc prolongation to a maximum of 480 msec (85). A 50-year-old man ingested 3120 mg and his QTc increased to 490, with nonspecific T-wave abnormalities peaking at 6 hours post-ingestion (86). Another case involved a 38-year-old woman who had taken 4020 mg of ziprasidone; she was also on quetiapine, gabapentin, venlafaxine, metformin, rofecoxib, and pravastatin but denied ingestions of these above her normal therapeutic dose. At 6 hours post ingestion, her QTc interval was 445, and her QRS duration was 111 (87).

Clozapine (Clozaril) first became available in 1989. It is the prototype atypical antipsychotic, but its use is limited to second-line therapy, owing to its propensity to cause fatal agranulocytosis (88), among other serious adverse effects including pulmonary embolism (89) and myocarditis (88, 90). Dose-dependent QTc prolongation has been demonstrated in feline hearts (91) and in human adults (92), in addition to other

^A Abstract received January 2004.

ECG abnormalities. One patient who had a QTc of 624 on clozapine improved to 504 msec after being switched to olanzapine (93). A 44-year-old man developed atrial and ventricular fibrillation after two weeks of clozapine therapy (94). Atrial fibrillation in a 69-year-old man has been reported (95). In children and adolescents, tachycardia has been noted; it is not known if this study specifically addressed the QTc parameter (96).

There are numerous reports of both fatal and nonfatal overdoses of clozapine, and there is evidence of increased risk of sudden death in patients taking therapeutic doses of clozapine compared with patients taking other psychiatric medications (88, 97).

Sertindole (Serdolect) is an atypical antipsychotic with a checkered past. When introduced in 1996, it was hailed as well-tolerated and efficacious in treating positive and negative symptoms of schizophrenia without extrapyramidal or other serious side effects. Unfortunately, reports of sudden death led to its removal from the market by the manufacturer in December 1998. A propensity to prolong the QT interval was known before the drug's large-scale introduction, but this prolongation was not as strongly associated with arrhythmias as might be expected (30, 98). Prolongation has been demonstrated in numerous studies and is dose-dependent (30, 99, 100). The mechanism of prolongation involves high-affinity antagonism of the HERG potassium channel (101). In a study of seven psychoactive drugs, sertindole was one of three – the others being pimozide and thioridazine – found to have very little selectivity of dopamine and serotonin blockade compared with affinity for HERG (5). The usage of sertindole remains controversial, as the clinical significance of prolongation is not known with certainty; for example, though one study demonstrated an increase in QTc during sertindole treatment as compared with treatment with a wide variety of other

antipsychotics, the authors argued that this increase is not clinically significant, in part because in 19.7 msec is less than the diurnal rate variation in normal subjects (30).

Aripiprazole^A (Abilify) is a recently-approved atypical antipsychotic with a unique pharmacologic mechanism called dopamine system stabilization; it has fewer adverse effects than many other antipsychotics (102). Clinically significant QTc prolongation has not been noted in any of several studies of adults (102-105). No studies of children specifically examining the QTc interval have been published. Kowatch and DelBello (106) recommend that clinicians be on the lookout for interactions with the cytochrome P450 systems 3A4 and 2D6 when prescribing this medication in children and adolescents with bipolar disorder.

Antipsychotics: traditional agents

PHENOTHIAZINES: THIORIDAZINE AND CHLORPROMAZINE.

Among the antipsychotics, thioridazine (Mellaril) has the greatest and best-documented propensity to prolong the QTc interval, due to its blockade of the delayed rectifier potassium channel (5, 107). It was this drug that was implicated in the first reports of sudden arrhythmic death on antipsychotics in 1963 (108). Since then, there have been numerous reports of TP (109, 110), QTc prolongation (111) in both therapeutic and overdoses (112), and an excess of sudden deaths (107, 113) and cardiotoxicity in overdose (114) as compared with other antipsychotics. QTc prolongation is dose-dependent (115-117). The mean increase in QTc has been measured at 33 to 35.8 msec, the longest of all the antipsychotics with the exception of intravenous droperidol (118).

223 cases of overdose with thioridazine have been summarized by Le Blaye et al (119), of which 23 occurred in children aged 12 years and under. 68 patients had ECG

^A Search completed October 2003.

changes, which included ventricular arrhythmias; third-degree block, especially in association with alcohol coingestion; and bundle branch block. These patients were more likely to have ingested higher doses than patients who did not have ECG changes. 17 of 223 patients had QT prolongation. TP was reported in only one case, that of an overdose, in which the patient had previously received amiodarone.

Thioridazine owes some of its electrocardiographic effects to its active metabolite mesoridazine (also sold separately as Serenitil). Both drugs' package inserts carry an FDA black-box warning – the most serious warning the agency can issue in a drug's labeling (120)– for dose-dependent prolongation of the QTc interval. Though it has been studied in children and adolescents for conduct disorder and schizophrenia, and is sometimes used in this population to treat psychosis, mania, aggression, agitation, autism, and self-injury (121), thioridazine is mainly indicated as third-line therapy in schizophrenic patients. However, some investigators have questioned the adequacy of the data to support avoiding its usage exclusively, given the propensity of other phenothiazines to prolong the QTc as well (122, 123).

Chlorpromazine (Thorazine), like thioridazine, is a phenothiazine, and as such may have the potential to cause ventricular arrhythmias including TP. Phenothiazines are thought to have their effect on the ECG by a mechanism similar to that of quinidine, which inhibits the delayed potassium rectifier current in myocytes and prolongs repolarization, as represented by the QT interval (124). Chlorpromazine has been shown to inhibit HERG potassium channels (125). It can do this at therapeutic dosages, in addition to causing other changes on the ECG (124), though it is unclear whether the effect is dose-dependent. Cases of TP have also been reported. One case occurred in a

female adult patient after long-term treatment, featuring a QTc prolongation to an astonishing 0.81 seconds; the TP resolved with discontinuation of the drug, and, interestingly, resumed when the drug was resumed (126). A review of the literature published in 2001 found only four reports of chlorpromazine-induced TP (including the aforementioned case), as well as several more ventricular arrhythmias, most of which included QTc prolongation. Electrolyte imbalances were noted in some cases, including hypokalemia, hypocalcemia, hyponatremia, and hypomagnesemia. There is a distinct female preponderance, which fits well with the longer baseline QTc in women. It is unclear whether this effect is relevant in children, as it is hypothesized that estrogen is responsible for the sex differences. None of these cases of chlorpromazine-induced arrhythmia occurred in children, and none could be found in the literature as of this writing.

BUTYROPHENONES: HALOPERIDOL AND DROPERIDOL

Like haloperidol (Haldol), droperidol (Inapsine) is an older typical butyrophenone antipsychotic. In children it is often used for rapid sedation of agitated patients in the acute setting (127, 128); it is not intended to be taken over the long term (129). Unlike haloperidol, however, droperidol has recently earned an FDA black-box warning similar to that of thioridazine about the potential for arrhythmia. The manufacturer reports that QTc prolongation, TP, and deaths have occurred in doses at and even below the therapeutic range, and recommends the droperidol be considered a second-line drug and, and avoided in patients with long QT on initial ECG screen and patients with a suggestive personal or family cardiac history (130). These recommendations are similar to those offered by Woollorton (131). Another study has demonstrated a dose-dependent

increase in QTc with intravenous droperidol (132). A 1996 review of cases of conduction disturbances in critically ill patients treated with droperidol concluded that the risk of QTc prolongation and arrhythmia was real, and that ECG monitoring at baseline and treatment should be done, that baseline serum magnesium and potassium should be checked and corrected, and that a 25% increase in the QTc after receiving droperidol is grounds for discontinuation of treatment (133).

Despite the black-box warning, however, recommendations to avoid droperidol altogether have been controversial. Some authors argue that it is unclear that the deaths referred to in the warning were related to droperidol, that no risk-benefit assessments have been performed analogous to those performed after thioridazine was singled out for danger, and that studies finding an increased QT interval were often done in very large doses (134).

Haloperidol has a somewhat less tarnished reputation in terms of cardiac effects than its sister butyrophenone, droperidol. One of the oldest antipsychotics, it is prescribed to children for the management of disorders including hyperactivity, autism, Tourette's syndrome, and obsessive-compulsive disorder. It is also used in the management of acute severe aggression, often as an intramuscular administration. Although cardiotoxicity is not common – extrapyramidal effects are much more prevalent and important – cardiac effects have been reported. There are a number of reports of TP and increased QTc in critically ill adults being treated with haloperidol. Cardiotoxicity tended not to become apparent below 1000 mg ingestions – hundreds of times the recommended dose – but in some individuals even therapeutic doses caused the problem. Many such cases were presaged by an elevated QTc, but in at least one report of a 66-

year-old woman who developed TP on therapeutic dose, this was not the case (135).

Another woman, aged 41, developed TP with a QTc of 610 msec only 55 minutes after receiving intravenous haloperidol (136). A crossover study in adults found no QTc prolongation compared to baseline during two weeks of treatment with haloperidol (137). A double-crossover study of 40 adult patients with Tourette's syndrome, in which haloperidol and pimozide were compared, found no QTc prolongation in the haloperidol-treated group (and only clinically nonsignificant prolongation in the pimozide group) (138). One series found an association of prolonged QTc and TP in adult intensive-care unit patients with pre-existing heart disease (139).

As of this writing, there have been no reported instances of TP or sudden deaths occurring in children treated with haloperidol. Pediatric overdosages have been reported, in which CNS symptoms dominate the presentation; in one series, in which eight children had ECGs done upon admission to the hospital after accidental haloperidol ingestion, two were said to have had a prolonged QT interval, but the degree of prolongation was not specified (140). Bradycardia, possibly secondary to drug-induced hypothermia, has been also reported in overdose involving 29-month-old and 11-month-old siblings (141).

Pimozide (Orap), a diphenylbutylpiperidine, is generally used as an alternative to haloperidol in treating Tourette's syndrome. It has been shown to be more effective than placebo in tic disorders, with fewer side effects than haloperidol (142). However, it too is associated with arrhythmias and dose-dependent QTc prolongation (138, 143, 144), probably because of its HERG potassium-channel blocking properties (5, 145). Sudden death at doses over 20 mg/day has been reported (146, 147). Most authorities recommend a baseline ECG before starting treatment with pimozide; while dosages are

being adjusted, avoiding dosage increases above a QTc that is 470 msec or more than 25% above baseline (148); at steady-state; and then every year (149). As with other drugs metabolized by the cytochrome P450 system, caution should also be exercised with regards to polypharmacy when prescribing pimozide, particularly with the macrolides: at least two sudden deaths have been reported in young adult subjects taking pimozide and clarithromycin at the same time (143). TP has been reported in a case of pimozide overdose in a 53-year-old woman (150).

There have been no case reports of sudden death or TP in children taking pimozide. Controlled studies of children have been few, and though at least one found no ECG abnormalities, this result is hardly reassuring in light of the small numbers of children studied. One open-label pilot study of eight boys between the ages of four and eight treated for three weeks with pimozide reported that ECG parameters remained within normal limits during weekly ECGs, but no details were given (151).

Alpha agonists

Originally developed as antihypertensives, the alpha agonists clonidine (Catapres) and guanfacine (Tenex) are being used to an increasing extent in psychiatry owing to their effects on central noradrenergic systems, and to an indirect extent the serotonergic and dopaminergic systems. Popular indications include second-line therapy for attention deficit-hyperactivity disorder and tic disorders after stimulants, tricyclics, and/or bupropion have failed, or in combination with methylphenidate (152). However, there are no FDA approvals for psychiatric indications, and data on the use of alpha agonists in children tends to come from uncontrolled studies, or controlled studies with a small number of subjects (152, 153). Although clonidine has been noted to produce ECG

changes, these are generally not considered dangerous in children without preexisting cardiac disease. There is more information on clonidine than on guanfacine in the literature, but it would be prudent to presume similar effects in guanfacine until more specific information is available.

That the alpha agonists should affect the heart follows from their mechanism of action. All adrenergic receptors inhibit the opening of voltage-gated Ca channels and activate K channels (154); alpha agonists strengthen such actions. The first reported episode of cardiotoxicity occurred in a 22-year-old woman, who experienced transient high-grade atrioventricular block in association with toxic levels of clonidine (155). Children taking clonidine either alone or in combination with other psychiatric medications have been reported to develop asymptomatic ECG abnormalities when the dosage was increased. These reverted with reduction of dosage, suggesting a threshold effect. Changes included sinus bradycardia, supraventricular premature complexes, intraventricular conduction delay, junctional escape ST and T-wave abnormalities, anterior ischemic changes, atrioventricular block, and QTc intervals ranging from 409 to 425 (2, 156, 157). The clinical significance of these changes is unclear, but are generally similar to expected electrophysiologic changes in adults (158). ECG changes reported in a child who was symptomatic with fatigue and sedation included hypotension and bradycardia, ST elevation, early repolarization, and junctional escape rhythm (2).

A retrospective examination of 42 children on either clonidine alone or clonidine plus a stimulant found that the ECG was as likely to normalize as to become abnormal during treatment, and thus that ECG changes were more likely attributable to normal changes in ECG over time, rather than to an effect of clonidine (159). The authors found

no prolongation of QTc over 440 msec. This finding should be interpreted with caution due to the small size of the study and inconsistencies in the time of day the ECGs were taken, but it suggests that studies purporting to find an effect of medications on the ECG should be viewed with caution in the absence of pretreatment ECGs. Unfortunately, little is known about the extent or causes of normal ECG variability in children, and the authors warn that it is difficult to disentangle drug-induced ECG changes from other causes of variation. They also point out that the lack of effect in this group does not rule out the possibility that some children may be highly affected. They call for replication with Holter monitoring, with ECGs at the same time of day, and with the same relationship to the time the medication was taken.

Clonidine overdose in adolescents has been reported to lead to labile blood pressure and sinus tachycardia without other ECG abnormalities, in the case of a 16-year-old girl who took approximately 6 mg clonidine; and bradycardia, in the case of an 18-year-old man who took 4 mg clonidine along with alcohol (160). Hypotension and bradycardia have been noted in many other pediatric overdoses (160-162). The only reported case of guanfacine overdose in a child (163) occurred in a two-year-old who ingested 4 mg; the only adverse event was a drop in blood pressure to 58 mm Hg systolic some hours after ingestion. This resolved without incident.

Abrupt discontinuation of clonidine leads to a well-recognized spectrum of cardiovascular and autonomic effects, including ST segment changes, QTc prolongation, and serious ventricular arrhythmia in adults (164). Sinus tachycardia and tachypnea were reported in a 10-year-old girl who missed a dose (2).

An association of clonidine or of clonidine and methylphenidate (Ritalin) with sudden death has been noted in at least four cases, but in each case there were circumstances making it difficult to ascribe the deaths to clonidine (165). In one case, blood analysis could detect neither drug, in two others, cardiac malformations were found, and in a third, death was blamed upon intentional fluoxetine overdose (165, 166). Recommendations to obtain a cardiac history and baseline and treatment ECGs have been controversial, owing to the uncertain benefit of these time-consuming measures in light of the rarity and uncertain causation of the deaths (158). Some experts feel that clonidine or clonidine plus methylphenidate are safe, while others warn against routine use of this combination (165).

Tricyclic antidepressants

Tricyclic antidepressants (TCAs), in use for over 50 years, have long been known to prolong the QTc interval in both adults and children. The most commonly used drugs of this class in children are imipramine, desipramine, nortriptyline, amitriptyline, and clomipramine. They are used for a variety of indications, including attention deficit-hyperactivity disorder, obsessive-compulsive disorder (clomipramine only), and enuresis. The primary noradrenergic mechanisms of TCAs involve blockade of norepinephrine reuptake, as well as binding to presynaptic alpha-2 receptors and increasing norepinephrine release; autonomic tone increases and raises the blood pressure and heart rate. Tricyclics also bind to and activate the postsynaptic alpha-1 receptor. Clomipramine has a similar uptake-blocking and postsynaptic-activating effects in the serotonergic system. Their anticholinergic side effects, which are more pronounced in the tertiary amines, can be attributed to their antagonism of muscarinic receptors;

however, these effects are less common in children than they are in adults. Finally, they block histaminic receptors. This blunderbuss nonspecificity is not confined to the central nervous system, as the TCAs' lipophilic structure allow for body-wide distribution. Cardiac side effects caused by therapeutic levels of TCAs include rise in blood pressure, increases in heart rate (by 20-25%), and in the ECG intervals PR (by 5-10%), QRS (by 7-25%), and QTc (by 3-10%) (167). These changes occur due to increased anticholinergic and noradrenergic tone in the cardiac conduction system, with inhibition of sodium influx specifically responsible for slowing propagation of depolarization and widening the QRS (168). Dose-response relationships are weak at low doses, but more evident at high doses or serum levels (169). Wilens et al's (33) detailed analysis of ECG changes found that the tricyclic causing the greatest increase from baseline QTc is probably imipramine, while desipramine appears to cause higher rates of incomplete intraventricular conduction. The authors concluded that these changes are likely to be of only minor clinical significance. Desipramine has also been shown to reduce heart rate variability in children, a circumstance that in some circumstances can predispose to arrhythmia (170).

TCAs, and particularly desipramine, have been associated with several sudden deaths in children and adolescents. A recent review of eight case reports (1) found that in six cases the child was taking desipramine, in one case imipramine and thioridazine, and in one case imipramine and dextroamphetamine. ECG data on these children prior to their deaths is scant, though one child reportedly had a QTc prolonged to 0.44-0.45 (baseline was 0.40) seven to fourteen months before death. Exercise immediately preceded cardiac arrest in four and possibly five cases. A study in response to the latter finding examined 9 pediatric and 13 adult subjects on desipramine with exercise testing,

and found modest elevations in blood pressure and heart rate, as well as an episode of ventricular tachycardia in a 31-year-old (171). Another study which examined 23 pediatric patients taking imipramine found no ventricular arrhythmias, supraventricular tachycardia, or atrioventricular conduction blocks during exercise testing (172). Desipramine was blamed in one death and imipramine in two others. One child had an abnormal coronary artery on autopsy. There was a family history of sudden deaths in young family members in the case of one child, and of other adverse cardiac events in the families of three others. The deaths were considered probably cardiac, but despite the TCAs' known cardiac effects, reports of TP are rare (173-178). One author proposed a mechanism of "reversed adrenaline" to explain the sudden deaths, arguing that blockade of alpha-adrenoreceptor-mediated vasoconstriction from a sudden endogenous or parenteral adrenaline load could have caused hypotensive collapse (179). Overdose may have been involved in several cases in which elevated levels of drug were found in postmortem blood samples; however, these elevations may have been factitious owing to postmortem changes (1). Due to the preponderance of desipramine or pro-desipramine in the deaths, some debate has centered around the use of this drug, with at least one author calling for its discontinuation in pediatrics (180) and others arguing that evidence of excessive danger is weak (181). Though these concerns are longstanding (182), there appear to be insufficient data at present to conclude that one tricyclic is definitely more or less harmful than the others (183). Given the small number of reports and the many confounding factors in those that do exist, a definite increased risk of sudden death in children taking tricyclics has not been established.

It is not a matter of dispute, however, that TCAs are cardiotoxic to all age groups in overdose. Hypotension is the commonest effect, but prolongation of the PR, QRS, and QTc occurs as well, as do ventricular arrhythmias (168, 184). There has been some research into the best way to stratify patients according to risk. In one series, children who presented with seizures were found to have the longest QTc prolongations (185). QRS duration may be more helpful than serum levels in predicting severity; one study found that QRS duration exceeding 160 msec in adult overdose patients was a significant predictor for risk of ventricular arrhythmias over a wide range of serum levels (186).

TREATMENT RECOMMENDATION GUIDELINES

A number of authorities have proposed sets of treatment recommendations which, if followed carefully, should reduce or minimize the risk of conduction-velocity changes or arrhythmias in children taking antipsychotics, alpha agonists, and tricyclic antidepressants. Briefly, these children should receive a thorough screening visit with careful attention to history of symptoms possibly referable to the heart, to family history, and to any other medications being taken; physical examination with vital signs; and baseline studies which, depending on the medication being considered, may include ECG, referral to a pediatric cardiologist, or laboratory measurements. Clinically significant changes in the EKG in children are generally felt to include the following: pulse < 60 or > 130 bpm, PR > 200 msec, QRS > 120 msec or > 25% change from baseline, or QTc > 450 msec (167, 187) (440 msec is a more conservative red flag). QTc prolongation by ≥ 60 msec should prompt concern (37), as should morphologic abnormalities such as T-wave inversions, U waves, or arrhythmias. Clinicians should be aware that these guidelines are not set in stone; for example, Moss (13) considers 460

msec to represent significant prolongation in children. **Tables 1 and 2** provide an overview and a summary guideline, respectively, for current recommendations regarding ECG monitoring in pediatric psychopharmacology, and based on the literature reviewed and clinical experience. **Table 3** summarizes relevant drug combinations of potential concern, as specifically pertaining to ECG safety. These tables should not be taken as definitive, but rather as guides, given that questions remain about the effects of these medications in pediatric patients.

PROSPECTIVE STUDY: STATEMENT OF PURPOSE AND HYPOTHESIS

The aims of this study were: (1) to assess the electrocardiographic (ECG) safety profile of low-dose ziprasidone (≤ 60 mg/day) among psychiatrically ill youths treated as outpatients for up to six months, and (2) to compare automated, machine-generated ECG parameters to those derived via manual measurement by a pediatric cardiologist blind to medication and dosage assignment.

The null hypotheses were as follows: a) low-dose ziprasidone does not cause clinically significant ECG changes in pediatric patients, and b) manual and automated measurements of ECG parameters do not significantly differ.

METHODS

This was an open-label, prospective clinical trial of ziprasidone in pediatric patients diagnosed with Tourette's syndrome (TS), obsessive-compulsive disorder (OCD), or a pervasive developmental disorder (PDD). Performed under an Investigational New Drug (IND) approval from the FDA in 1999 for the treatment of refractory cases, the study

took place in 2000. This study was designed by Andrés Martín to examine the drug's electrocardiographic safety profile in children and adolescents by using small doses and emphasizing close ECG monitoring. It was performed by Andrés Martín and Lawrence Scahill, and by staff members under their supervision. All data were collated by Jennifer Blair. Statistical approach to data analysis was done by Andrés Martín and Jennifer Blair.

SUBJECT ELIGIBILITY

Male and female subjects aged 7 to 19 were eligible for participation in the study if they met the following inclusion criteria: (1) DSM-IV diagnosis of TS, OCD, or a PDD, based on a standard clinical evaluation and corroborated through appropriate structured diagnostic interviews, such as the child and adolescent version of the Schedule for Affective Disorders and Schizophrenia (K-SADS)(188), the Autism Diagnostic Interview-Revised (ADI-R)(189), or the Autism Diagnostic Observation Schedule (ADOS)(190, 191); (2) at least “moderate” symptomatic severity, as indicated by a clinical global impression (CGI) rating of ≥ 4 (192); (3) symptom severity score of ≥ 1.5 SD above clinically established norms in the primary outcome measure specific for the disorder (Yale Global Tic Severity Scale (YGTSS)(193), Children's Yale-Brown Obsessive Compulsive Scale (Y-BOCS)(194), or Aberrant Behavior Checklist (ABC)(195-197); (4) evidence of failure on at least one atypical antipsychotic medication such as risperidone, as defined by either less than 30% symptom reduction in the primary outcome measure, and/or unacceptable side effects requiring drug discontinuation – weight gain in excess of 2 kg/month being the more common, and occurring in 6 of 20 participants; and (5) at least 2 weeks since treatment with another neuroleptic was

discontinued (4 weeks for depot neuroleptics). In addition, subjects were required to have a mental age of at least three years. Intelligence was assessed in verbal children with the Wechsler Intelligence Schedule for Children-III (WISC-III)(198), and in nonverbal children with the Leiter International Performance Scales, Revised (199). The Vineland Adaptive Behavior Scales were used to assess adaptive functioning (200). Mental retardation was defined as WISC or Leiter IQ scores < 70 , and Vineland adaptive scores in the deficient range.

Subjects were required to weigh at least 20 kg and be free of major medical conditions such as heart disease, hypertension, liver or renal failure, pulmonary disease, or unstable seizure disorder identified by history, physical examination or laboratory tests, including ECG, at the screening visit. Baseline QTc interval was required to be < 450 msec. Postmenarchal females required a negative serum human chorionic gonadotrophin test to rule out pregnancy. Concurrent psychotropic medication was exclusionary, except for previous selective serotonin reuptake inhibitor use in 4 subjects (fluoxetine in 3, sertraline in 1).

All pediatric patients were enrolled through the Yale Child Study Center's pediatric psychopharmacology clinic. As part of the IND from the FDA, adults were also to be enrolled in the study. After a full description of the study and of available treatment alternatives, subjects' parents or caregivers (or, if adults, the subjects themselves) signed written informed consent. When feasible, informed assent was obtained from the patients themselves. The study and its consent documents were approved by the Yale University School of Medicine's Institutional Review Board.

STUDY DESIGN AND DOSING SCHEDULE

The trial was originally planned as a one-year, prospective, open-label design. On Day 1, subjects received 5 mg of ziprasidone to be taken at bedtime with food. The dose was raised by 5 mg every 4-6 days in the first month as tolerated, or to a target maximum of 20 mg BID. After the first month, the dosage was raised or lowered according to clinical judgement. The low dosage, agreed upon with the FDA, was intended to emphasize safety and was to be a prelude to studies at higher clinical doses. See **Table 4** for a sample dosing schedule. Subjects older than 18 years old were permitted to exceed it, and the highest dosage reached was 30 mg BID by one nineteen-year-old female. Primary caregivers administered all study medications in a divided morning and bedtime oral dosing schedule. A baseline, pre-medication electrocardiogram was obtained at the outset of the study, and repeated at weeks 1, 2, 3, 4, 6, 8, 12, and monthly thereafter. ECGs, except for several obtained off-site during patient vacations or other logistic conflicts, were obtained with a Hewlett Packard XLI PageWriter electrocardiographic machine at the pediatric cardiology laboratory at Yale-New Haven Children's Hospital. Its ECG analysis program uses the Bazett formula (QT divided by the square root of the R-R interval) to calculate QT_c values. Printouts of twelve-lead ECGs were sent to eResearch Technologies in Philadelphia, PA, where two technicians and a board-certified pediatric cardiologist performed manual measurements designed to obtain accurate and reliable QT_c intervals.

DATA ANALYSIS

Statistical analysis involved comparison of each subject's baseline and peak values of manually-measured QT_c intervals using paired t-tests. Results are reported as absolute

(msec) and relative (%) changes, are expressed as mean $\pm$ standard deviation (SD), and considered significant at $p < 0.05$. Pearson's correlation coefficients were computed to compare ECG intervals derived through manual or automatic means, as well as the relationship between dose and QTc interval change. The kappa coefficient was used to evaluate the agreement between automated and manually-assessed QTc prolongation (using ≥ 440 msec as cutoff). The chi-square test was used to compare the proportion of subjects in our study with prolongation to the proportion with prolongation in a study done by the manufacturer (see **Table 8**), with Fisher's exact test used for cells whose value was 1. The SAS program was used for all calculations.

RESULTS

SUBJECTS

An adult patient enrolled under the same IND unexpectedly died during the course of the trial, of causes eventually deemed to be unrelated to ziprasidone. Pending autopsy results and a full postmortem investigation, the trial was discontinued, in close consultation with the Institutional Review Board at Yale as well as with representatives from the FDA. The specifics of this death are detailed in Scahill, Blair & Martin (2004, in preparation), and all clinical data of that individual (including ECG data) are not included as part of this report.

Prior to the study's premature discontinuation, 20 patients were enrolled, each of whom received at least a baseline and one follow-up ECG. Sixteen participants were boys, four girls; sixteen were Caucasian, three Hispanic, and one African-American; their mean age was 13.2 ± 3.0 years (range, 8 to 19). Nine subjects carried a primary

diagnosis of TS, four of OCD, and seven of PDD. One subject with OCD had a comorbid tic disorder, as did one with PDD; two with TS also had OCD, and one with PDD had both comorbid OCD and a tic disorder. Other secondary diagnoses included learning disorders, attention deficit-hyperactivity disorder, and oppositional-defiant disorder. Six of the seven children with PDD had mental retardation.

Although clinical efficacy data were collected alongside the safety data, these are not reported here (Scahill et al, in preparation). When the study was prematurely discontinued, 20 subjects had been recruited out of a target number of 30, and each had been followed for, on average, fewer than six months out of a target duration of one year. Only the results of the ECG investigations are reported here.

Subjects were treated with a mean ziprasidone dose of 30 ± 13 mg/day (range, 30 to 60), and were followed for 4.6 ± 2.0 months (range, 0.7 to 6), during which a median of 9 ECGs were obtained per subject (range, 2 to 11). This yielded a total of 176 ECGs that were manually analyzed.

MEASUREMENT METHODS

A weak correlation between QTc prolongation and ziprasidone dose was detected when using automatically-derived values ($r = 0.203$, $p < 0.01$), but was no longer evident when using manually-calculated means ($r = 0.159$, $p = 0.07$). The two measurement methods were correlated with each other ($r = 0.52$, $p < 0.0001$), but as depicted in the scatterplot of **Figure 1**, many outliers were readily apparent, particularly around extremes of the value range.

Among the 176 ECGs available for analysis, there were 134 (76%) for which both manual and automated measurements of QTc were obtained. In 17 (13%) of these, a

prolonged QTc (defined as ≥ 440 msec) was detected by either automated or manual measurement. Among these, only 3 were considered prolonged by both manual and automated methods (percent agreement, 18%; $\kappa = 0.25$), indicating only minimal improvement over the amount of agreement expected by chance alone (201). Using manual measurements as the gold standard, the machine's sensitivity for prolongation was 25%, while its specificity was 95%. See **Table 5**.

ELECTROCARDIOGRAPHIC PARAMETERS (MANUAL MEASUREMENTS)

The mean QTc interval increase from the baseline to the peak value was 28 ± 26 msec (representing a $7 \pm 8\%$ increase). The maximum increase from baseline was 114 msec. No patient's QTc ever exceeded 500 msec; the highest observed value was 470 msec. There were also statistically significant changes from baseline to peak values in heart rate and in the PR interval ($p < 0.01$ for each), but not in QRS complex width ($p = 0.87$). These results are summarized in **Table 6**. Eight patients experienced QTc prolongations of ≥ 440 msec while on ziprasidone; three of those had episodes ≥ 450 msec. See **Table 7**. A comparison of the number of subjects who experienced changes from baseline of ≥ 30 , 60, or 75 msec with the same result from the manufacturer's study of ziprasidone is shown in **Table 8**. A chi-squared test found no significant difference between the number of subjects with prolongation in our study versus the manufacturer's; this is represented on the table by the p value of the test results.

DISCUSSION

The part of this study concerned with measurement of the QTc found a poor agreement between methods in detecting QTc prolongation. In light of the likelihood that

clinicians often rely upon automatic numbers, this is concerning, as is the 25% sensitivity of the machine – indicating the machine “missed” 75% of prolongation “events” greater than or equal to 440 msec, although its high specificity suggests that when it detects prolongation, manual confirmation may not be necessary. The null hypothesis of no difference between the methods is rejected. It would seem necessary to advise – or remind – clinicians to mistrust the numbers that appear on an ECG printout, particularly the QTc. Again, this is not a new finding; many authors have discussed the inherent weaknesses of automated measurements of this interval (11, 22, 31, 32). Because manual measurement of the QTc trumps the software, psychiatrists who obtain ECGs would be well-advised to send them to an experienced cardiologist, who will be familiar with the careful methods of measurement that are delineated by, for example, Anderson (11) and Al-Khatib (38). The growing ease of electronic data transmission may make this simpler in the future, but at present many ECG machines are not linked to the Internet, and clinicians may need to make use of fax machines, at times sacrificing some precision along the way.

With regards to QTc prolongation, this study demonstrates that treatment with ziprasidone is associated with increases over baseline of the QTc interval in children and adolescents. This increase is greater (mean, 28 ± 26 msec) than that demonstrated in studies of adults, which found a mean of 20.6 msec (76) or 11 msec (78) increases over baseline. It is consistent with another group’s demonstration of QTc prolongation from baseline by 17.3 msec in eight adolescent patients treated with ziprasidone (81). Apart from inherent difficulties in interpretation of the QTc, the study was limited by a small sample size, lack of placebo control (preventing comparisons with the manufacturer’s

finding in adults of a 10 msec increase versus placebo (76)), open-label design, unbalanced gender ratio, heterogeneous ages and diagnoses, and premature discontinuation. Automated measurement data were lacking for some ECGs, which weakens our analysis of the differences between manual and automated measurements. Only one baseline ECG was obtained for each patient, which may or may not represent a true personal baseline.

Despite these limitations, there are several reasons to be concerned by our study results. The mean increase among these 20 pediatric subjects is greater than a value which led the FDA to mandate a boldface warning in ziprasidone's package labeling. Eight subjects experienced prolongations on at least one occasion of ≥ 440 msec, a reasonable threshold for caution (24, 26, 27, 33, 34), and three of ≥ 450 msec, a value concerning enough to have excluded candidates from our study if present at screening. One child experienced prolongation of 114 msec while on ziprasidone, which is well over both the 75 msec increase suggested by Morganroth (27) as clinically significant in adults, and the 60-msec increase set by the The Committee for Proprietary Medicinal Products (37) as significant for risk of arrhythmia. Based upon that prolongation, and upon the fact that three of 20 subjects experienced episodes of prolongation ≥ 450 msec, we can reject the null hypothesis regarding ziprasidone and conclude that in low doses it does cause clinically significant prolongation in the QTc in pediatric patients. Finally, all of these findings occurred at low dosage. Though we did not demonstrate statistically significant dose dependence, other studies have found this phenomenon in adults (77). If this phenomenon does hold in children, and if peak increases at doses of 40-60 mg/day

were 28 msec, they might be much greater at today's doses, which often range from 80-160 mg/day (Andrés Martin, personal communication).

A note on calculations should be made. Depending upon how other studies derived their numbers representing prolongation, our result may be more conservative and risks a type I error. For each patient, we obtained a value of maximum prolongation by subtracting the unmedicated value of QTc from the single highest value of QTc attained while on drug. We then summed these numbers and divided by our n of 20 to obtain 28 msec. It is possible that other studies obtained their mean number by comparing each patient's baseline to not just his highest value, but to all higher values of QTc; or even all other values of QTc, including those that dropped *below* baseline; and dividing by total number of ECGs rather than total number of patients. Sources describing the manufacturer's study of ziprasidone do not make this distinction clear (76, 77). Neither does the study that found an 11 msec increase (78). Because our priority was to avoid a type II error – that of failing to reject the null hypothesis due to missing prolongation – we felt it prudent to look at peak values of QTc rather than averaging all increases together, since if it only takes one episode of prolongation to put a patient at risk, then a drug's maximum capacity to prolong the QTc is more important than what it does on average. This methodology may, however, run the risk of incurring a type I error – that of finding an effect erroneously and falsely rejecting the null hypothesis.

On a mechanistic note, in light of ziprasidone's probable mechanism of prolongation – that of blockade of the fast component of the delayed rectifier potassium channel (5) – it is interesting to consider that statistically significant prolongation of the QRS interval was not found in our subjects. The channel, encoded by the HERG gene, is

important during repolarization, but not depolarization – the latter being represented on the ECG by the QRS complex. Our findings lend strength to the idea that HERG blockade during repolarization is predominantly responsible for QTc prolongation by ziprasidone.

Though there were too few females in our study for a subgroup analysis, it is interesting to note that the subject with the longest baseline and medicated QTc intervals – often in the 440s – was a nineteen-year-old female. The QTc is known to be longer in postpubertal women than in men (10, 14, 25); possibly this effect applies to adolescent girls. Another possible explanation for prolongation in our subject could be related to dose, since her doses ranged up to 60 mg/day, unlike the other subjects whose maximum was 40 mg/day. Again, however, we did not detect a significant dose-response effect in this small study.

Because of the mean degree of peak prolongation, the fact that 3 of 20 children had prolongations over 450 msec and one had a 114-msec prolongation, and the fact that these changes occurred at low doses when a dose-dependent effect on prolongation has been noted in adults (77), clinicians must carefully weigh the decision to use ziprasidone. They may want to consider reserving it as a second- or third-line drug, particularly in patients with underlying risk factors for QTc prolongation, and particularly in light of the high doses that are standard in current practice and the risk of overdose. They will have to balance this possible increased risk of arrhythmia and sudden death with the evidence that ziprasidone may have fewer adverse effects, such as weight gain (75), than other drugs of its kind. Should they decide to use ziprasidone, clinicians should take precautions to avoid missing drug-induced QTc prolongation or a baseline congenital

prolongation. They are strongly advised to screen and monitor patients taking ziprasidone with ECGs according to clinical guidelines, including careful history-taking, sensible ECG practices, and consultation with a pediatric cardiologist for interpretation and for manual measurement of the QTc interval.

REFERENCES

1. Varley, C.K. 2001. Sudden death related to selected tricyclic antidepressants in children: epidemiology, mechanisms and clinical implications. *Paediatr Drugs*. 3(8): 613-627.
2. Cantwell, D.P., Swanson, J. and Connor, D.F. 1997. Case study: adverse response to clonidine. *J Am Acad Child Adolesc Psychiatry*. 36(4): 539-544.
3. Viskin, S. 1999. Long QT syndromes and torsade de pointes. *Lancet*. 354(9190): 1625-1633.
4. Hancox, J.C. and Witchel, H.J. 2000. Psychotropic drugs, HERG, and the heart. *Lancet*. 356(9227): 428.
5. Kongsamut, S., Kang, J., Chen, X.L., Roehr, J. and Rampe, D. 2002. A comparison of the receptor binding and HERG channel affinities for a series of antipsychotic drugs. *Eur J Pharmacol*. 450(1): 37-41.
6. Keating, M.T. and Sanguinetti, M.C. 1996. Molecular genetic insights into cardiovascular disease. *Science*. 272(5262): 681-685.
7. Bennett, P.B., Yazawa, K., Makita, N. and George, A.L., Jr. 1995. Molecular mechanism for an inherited cardiac arrhythmia. *Nature*. 376(6542): 683-685.
8. Priori, S.G., Barhanin, J., Hauer, R.N., Haverkamp, W., Jongsma, H.J., *et al*. 1999. Genetic and molecular basis of cardiac arrhythmias: impact on clinical management parts I and II. *Circulation*. 99(4): 518-528.
9. Surawicz, B. 1996. Will QT dispersion play a role in clinical decision-making? *J Cardiovasc Electrophysiol*. 7(8): 777-784.
10. Bednar, M.M., Harrigan, E.P., Anziano, R.J., Camm, A.J. and Ruskin, J.N. 2001. The QT interval. *Prog Cardiovasc Dis*. 43(5 Suppl 1): 1-45.
11. Anderson, M.E., Al-Khatib, S.M., Roden, D.M. and Califf, R.M. 2002. Cardiac repolarization: current knowledge, critical gaps, and new approaches to drug development and patient management. *Am Heart J*. 144(5): 769-781.
12. Dessertenne, F. 1966. [Ventricular tachycardia with 2 variable opposing foci]. *Arch Mal Coeur Vaiss*. 59(2): 263-272.
13. Taylor, D.M. 2003. Antipsychotics and QT prolongation. *Acta Psychiatr Scand*. 107(2): 85-95.

14. Moss, A.J. 1993. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. *Am J Cardiol.* 72(6): 23B-25B.
15. Morganroth, J. 1993. Relations of QTc prolongation on the electrocardiogram to torsades de pointes: definitions and mechanisms. *Am J Cardiol.* 72(6): 10B-13B.
16. Welch, R. and Chue, P. 2000. Antipsychotic agents and QT changes. *J Psychiatry Neurosci.* 25(2): 154-160.
17. Bazett, H. 1918. An analysis of the time-relations of electrocardiograms. *Heart.* 7: 353-370.
18. Batchvarov, V. and Malik, M. 2002. Individual patterns of QT/RR relationship. *Card Electrophysiol Rev.* 6(3): 282-288.
19. Funck-Brentano, C. and Jaillon, P. 1993. Rate-corrected QT interval: techniques and limitations. *Am J Cardiol.* 72(6): 17B-22B.
20. de Bruyne, M.C., Hoes, A.W., Kors, J.A., Hofman, A., van Bommel, J.H., *et al.* 1999. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. *Eur Heart J.* 20(4): 278-284.
21. el-Gamal, A., Gallagher, D., Nawras, A., Gandhi, P., Gomez, J., *et al.* 1995. Effects of obesity on QT, RR, and QTc intervals. *Am J Cardiol.* 75(14): 956-959.
22. Malik, M. and Camm, A.J. 2001. Evaluation of drug-induced QT interval prolongation: implications for drug approval and labelling. *Drug Saf.* 24(5): 323-351.
23. Cowan, J.C., Yusoff, K., Moore, M., Amos, P.A., Gold, A.E., *et al.* 1988. Importance of lead selection in QT interval measurement. *Am J Cardiol.* 61(1): 83-87.
24. Garson, A., Jr. 1993. How to measure the QT interval--what is normal? *Am J Cardiol.* 72(6): 14B-16B.
25. Rautaharju, P.M., Zhou, S.H., Wong, S., Calhoun, H.P., Berenson, G.S., *et al.* 1992. Sex differences in the evolution of the electrocardiographic QT interval with age. *Can J Cardiol.* 8(7): 690-695.
26. Vervaet, P. and Amery, W. 1993. Reproducibility of QTc-measurements in healthy volunteers. *Acta Cardiol.* 48(6): 555-564.
27. Morganroth, J., Brozovich, F.V., McDonald, J.T. and Jacobs, R.A. 1991. Variability of the QT measurement in healthy men, with implications for selection

of an abnormal QT value to predict drug toxicity and proarrhythmia. *Am J Cardiol.* 67(8): 774-776.

28. Mezzacappa, E., Tremblay, R.E., Kindlon, D., Saul, J.P., Arseneault, L., *et al.* 1997. Anxiety, antisocial behavior, and heart rate regulation in adolescent males. *J Child Psychol Psychiatry.* 38(4): 457-469.
29. Molnar, J., Zhang, F., Weiss, J., Ehlert, F.A. and Rosenthal, J.E. 1996. Diurnal pattern of QTc interval: how long is prolonged? Possible relation to circadian triggers of cardiovascular events. *J Am Coll Cardiol.* 27(1): 76-83.
30. Pezawas, L., Quiner, S., Moertl, D., Tauscher, J., Barnas, C., *et al.* 2000. Efficacy, cardiac safety and tolerability of sertindole: a drug surveillance. *Int Clin Psychopharmacol.* 15(4): 207-214.
31. Miller, M.D., Porter, C. and Ackerman, M.J. 2001. Diagnostic accuracy of screening electrocardiograms in long QT syndrome I. *Pediatrics.* 108(1): 8-12.
32. Kautzner, J. 2002. QT interval measurements. *Card Electrophysiol Rev.* 6(3): 273-277.
33. Wilens, T.E., Biederman, J., Baldessarini, R.J., Geller, B., Schleifer, D., *et al.* 1996. Cardiovascular effects of therapeutic doses of tricyclic in children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 35(11): 1491-1501.
34. Moss, A.J. and Schwartz, P.J. 1982. Delayed repolarization (QT or QTU prolongation) and malignant ventricular arrhythmias. *Mod Concepts Cardiovasc Dis.* 51(3): 85-90.
35. Vincent, G.M., Timothy, K.W., Leppert, M. and Keating, M. 1992. The spectrum of symptoms and QT intervals in carriers of the gene for long-QT syndrome. *N Engl J Med.* 327(12): 846-852.
36. Priori, S.G., Schwartz, P.J., Napolitano, C., Bloise, R., Ronchetti, E., *et al.* 2003. Risk stratification in the long-QT syndrome. *N Engl J Med.* 348(19): 1866-1874.
37. Committee for Proprietary Medicinal Products. *Points to Consider: The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products.* 1997. London, England: Human Medicines Evaluation Unit.
38. Al-Khatib, S.M., LaPointe, N.M., Kramer, J.M. and Califf, R.M. 2003. What clinicians should know about the QT interval. *J Amer Med Assoc.* 289(16): 2120-2127.

39. Labellarte, M.J., Crosson, J.E. and Riddle, M.A. 2003. The relevance of prolonged QTc measurement to pediatric psychopharmacology. *J Am Acad Child Adolesc Psychiatry*. 42(6): 642-650.
40. Posey, D.J., Walsh, K.H., Wilson, G.A. and McDougale, C.J. 1999. Risperidone in the treatment of two very young children with autism. *J Child Adolesc Psychopharmacol*. 9(4): 273-276.
41. Gesell, L.B. and Stephen, M. 1997. Toxicity following a single dose of risperidone for pediatric attention deficit hyperactivity disorder (ADHD). *J Toxicol Clin Toxicol*. 35: 549.
42. Ravin, D.S. and Levenson, J.W. 1997. Fatal cardiac event following initiation of risperidone therapy. *Ann Pharmacother*. 31(7-8): 867-870.
43. Brown, K., Levy, H., Brenner, C., Leffler, S. and Hamburg, E.L. 1993. Overdose of risperidone. *Ann Emerg Med*. 22(12): 1908-1910.
44. Lo Vecchio, F., Hamilton, R.J. and Hoffman, R.J. 1996. Risperidone overdose. *Am J Emerg Med*. 14(1): 95-96.
45. Catalano, G., Catalano, M.C. and Taylor, W. 1997. Acute risperidone overdose. *Clin Neuropharmacol*. 20(1): 82-85.
46. Acri, A.A. and Henretig, F.M. 1998. Effects of risperidone in overdose. *Am J Emerg Med*. 16(5): 498-501.
47. Moore, N.C. and Shukla, P. 1997. Risperidone overdose. *Am J Psychiatry*. 154(2): 289-290.
48. Cheslik, T.A. and Erramouspe, J. 1996. Extrapyramidal symptoms following accidental ingestion of risperidone in a child. *Ann Pharmacother*. 30(4): 360-363.
49. Catalano, G., Catalano, M.C., Nunez, C.Y. and Walker, S.C. 2001. Atypical antipsychotic overdose in the pediatric population. *J Child Adolesc Psychopharmacol*. 11(4): 425-434.
50. Burns, M.J. 2001. The pharmacology and toxicology of atypical antipsychotic agents. *J Toxicol Clin Toxicol*. 39(1): 1-14.
51. Shaw, J.A., Lewis, J.E., Pascal, S., Sharma, R.K., Rodriguez, R.A., *et al*. 2001. A study of quetiapine: efficacy and tolerability in psychotic adolescents. *J Child Adolesc Psychopharmacol*. 11(4): 415-424.

52. Czekalla, J., Beasley, C.M., Jr., Dellva, M.A., Berg, P.H. and Grundy, S. 2001. Analysis of the QTc interval during olanzapine treatment of patients with schizophrenia and related psychosis. *J Clin Psychiatry*. 62(3): 191-198.
53. Dineen, S., Withrow, K., Voronovitch, L., Munshi, F., Nawbary, M.W., *et al.* 2003. QTc prolongation and high-dose olanzapine. *Psychosomatics*. 44(2): 174-175.
54. Kosky, N. 2002. A possible association between high normal and high dose olanzapine and prolongation of the PR interval. *J Psychopharmacol*. 16(2): 181-182.
55. Catalano, G., Cooper, D.S., Catalano, M.C. and Butera, A.S. 1999. Olanzapine overdose in an 18-month-old child. *J Child Adolesc Psychopharmacol*. 9(4): 267-271.
56. Bond, G.R. and Thompson, J.D. 1999. Olanzapine pediatric overdose. *Ann Emerg Med*. 34(2): 292-293.
57. Chambers, R.A., Caracansi, A. and Weiss, G. 1998. Olanzapine overdose cause of acute extrapyramidal symptoms. *Am J Psychiatry*. 155(11): 1630-1631.
58. Kochhar, S., Nwokike, J.N., Jankowitz, B., Sholevar, E.H., Abed, T., *et al.* 2002. Olanzapine overdose: a pediatric case report. *J Child Adolesc Psychopharmacol*. 12(4): 351-353.
59. Fogel, J. and Diaz, J.E. 1998. Olanzapine overdose. *Ann Emerg Med*. 32(2): 275-276.
60. Cohen, L.G., Fatalo, A., Thompson, B.T., Di Centes Bergeron, G., Flood, J.G., *et al.* 1999. Olanzapine overdose with serum concentrations. *Ann Emerg Med*. 34(2): 275-278.
61. O'Malley, G.F., Seifert, S., Heard, K., Daly, F. and Dart, R.C. 1999. Olanzapine overdose mimicking opioid intoxication. *Ann Emerg Med*. 34(2): 279-281.
62. Dougherty, T.J., Greene, T.F., Farrell, S.E. and Roberts, J.R. 1997. Adult and pediatric olanzapine (Zyprexa) overdose. *J Toxicol Clin Toxicol*. 35: 550.
63. Powell, G., Nelson, L. and Hoffman, R. 1997. Overdose with Olanzapine (Zyprexa), a new antipsychotic agent. *J Toxicol Clin Toxicol*. 35: 550.
64. Cadario, B. 2000. Olanzapine (Zyprexa): suspected serious reactions. *Can Med Assoc J*. 163(1): 85-86, 89-90.

65. McConville, B.J., Arvanitis, L.A., Thyrum, P.T., Yeh, C., Wilkinson, L.A., *et al.* 2000. Pharmacokinetics, tolerability, and clinical effectiveness of quetiapine fumarate: an open-label trial in adolescents with psychotic disorders. *J Clin Psychiatry*. 61(4): 252-260.
66. Catalano, G., Catalano, M.C., Agustines, R.E., Dolan, E.M. and Paperwalla, K.N. 2002. Pediatric quetiapine overdose: a case report and literature review. *J Child Adolesc Psychopharmacol*. 12(4): 355-361.
67. Juhl, G.A., Benitez, J.G. and McFarland, S. 2002. Acute quetiapine overdose in an eleven-year-old girl. *Vet Hum Toxicol*. 44(3): 163-164.
68. Gajwani, P., Pozuelo, L. and Tesar, G.E. 2000. QT interval prolongation associated with quetiapine (Seroquel) overdose. *Psychosomatics*. 41(1): 63-65.
69. Litovitz, T.L., Klein-Schwartz, W., Caravati, E.M., Youniss, J., Crouch, B., *et al.* 1999. 1998 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*. 17(5): 435-487.
70. Keck, P.E., Jr., Reeves, K.R. and Harrigan, E.P. 2001. Ziprasidone in the short-term treatment of patients with schizoaffective disorder: results from two double-blind, placebo-controlled, multicenter studies. *J Clin Psychopharmacol*. 21(1): 27-35.
71. Arato, M., O'Connor, R. and Meltzer, H.Y. 2002. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. *Int Clin Psychopharmacol*. 17(5): 207-215.
72. Daniel, D.G., Zimbroff, D.L., Potkin, S.G., Reeves, K.R., Harrigan, E.P., *et al.* 1999. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Ziprasidone Study Group. *Neuropsychopharmacology*. 20(5): 491-505.
73. Schmidt, A.W., Lebel, L.A., Howard, H.R., Jr. and Zorn, S.H. 2001. Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. *Eur J Pharmacol*. 425(3): 197-201.
74. Seeger, T.F., Seymour, P.A., Schmidt, A.W., Zorn, S.H., Schulz, D.W., *et al.* 1995. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. *J Pharmacol Exp Ther*. 275(1): 101-113.
75. Allison, D.B., Mentore, J.L., Heo, M., Chandler, L.P., Cappelleri, J.C., *et al.* 1999. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 156(11): 1686-1696.

76. Anonymous. Pfizer, Inc. 2002. Package insert, Geodon (ziprasidone). http://www.pfizer.com/download/uspi_geodon.pdf. (Accessed September 4, 2003)
77. Gordon, M. Food and Drug Administration -- Center for Drug Evaluation and Research, Division of CardioRenal Drug Products. 2000. Ziprasidone, NDA #20825: Study report of Clinical Pharmacology Protocol #128-054. <http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1b.pdf>. (Accessed March 3, 2004)
78. Keck, P.E., Jr., Versiani, M., Potkin, S., West, S.A., Giller, E., *et al.* 2003. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry*. 160(4): 741-748.
79. Goodnick, P.J. 2001. Ziprasidone: profile on safety. *Expert Opin Pharmacother*. 2(10): 1655-1662.
80. Sallee, F.R., Kurlan, R., Goetz, C.G., Singer, H., Scahill, L., *et al.* 2000. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry*. 39(3): 292-299.
81. Malone, R.P., Delaney, M.A. and Gifford, C. *Ziprasidone treatment-associated changes in QTc and weight in adolescents with autism*. in *American Academy of Child and Adolescent Psychiatry*. 2004. Miami, FL. (Abstr.)
82. McDougale, C.J., Kem, D.L. and Posey, D.J. 2002. Case series: use of ziprasidone for maladaptive symptoms in youths with autism. *J Am Acad Child Adolesc Psychiatry*. 41(8): 921-927.
83. Patel, N.C., Sierk, P., Dorson, P.G. and Crismon, L. 2002. Experience with ziprasidone. *J Am Acad Child Adolesc Psychiatry*. 41(5): 495.
84. Bryant, S.M., Zilberstein, J., Cumpston, K.L., Magdziarz, D.D. and Costerisan, D. 2003. A case series of ziprasidone overdoses. *Vet Hum Toxicol*. 45(2): 81-82.
85. Biswas, A.K., Zabrocki, L.A., Mayes, K.L. and Morris-Kukoski, C.L. 2003. Cardiotoxicity associated with intentional ziprasidone and bupropion overdose. *J Toxicol Clin Toxicol*. 41(2): 101-104.
86. Burton, S., Heslop, K., Harrison, K. and Barnes, M. 2000. Ziprasidone overdose. *Am J Psychiatry*. 157(5): 835.
87. House, M. 2002. Overdose of ziprasidone. *Am J Psychiatry*. 159(6): 1061-1062.

88. Trenton, A., Currier, G. and Zwemer, F. 2003. Fatalities associated with therapeutic use and overdose of atypical antipsychotics. *CNS Drugs*. 17(5): 307-324.
89. Suttman, I., Dittert, S., Landgraf, R., Schulze, J., Folwaczny, C., *et al.* 2000. Clozapine and sudden death. *Lancet*. 355(9206): 842-843; author reply 843.
90. Warner, B., Alphs, L., Schaedelin, J. and Koestler, T. 2000. Clozapine and sudden death. *Lancet*. 355(9206): 842; author reply 843.
91. Tie, H., Walker, B.D., Singleton, C.B., Bursill, J.A., Wyse, K.R., *et al.* 2001. Clozapine and sudden death. *J Clin Psychopharmacol*. 21(6): 630-632.
92. Kang, U.G., Kwon, J.S., Ahn, Y.M., Chung, S.J., Ha, J.H., *et al.* 2000. Electrocardiographic abnormalities in patients treated with clozapine. *J Clin Psychiatry*. 61(6): 441-446.
93. Cohen, H., Loewenthal, U., Matar, M.A. and Kotler, M. 2001. Reversal of pathologic cardiac parameters after transition from clozapine to olanzapine treatment: a case report. *Clin Neuropharmacol*. 24(2): 106-108.
94. Varma, S. and Achan, K. 1999. Dysrhythmia associated with clozapine. *Aust N Z J Psychiatry*. 33(1): 118-119.
95. Low, R.A., Jr., Fuller, M.A. and Popli, A. 1998. Clozapine induced atrial fibrillation. *J Clin Psychopharmacol*. 18(2): 170.
96. Kumra, S., Frazier, J.A., Jacobsen, L.K., McKenna, K., Gordon, C.T., *et al.* 1996. Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Arch Gen Psychiatry*. 53(12): 1090-1097.
97. Modai, I., Hirschmann, S., Rava, A., Kurs, R., Barak, P., *et al.* 2000. Sudden death in patients receiving clozapine treatment: a preliminary investigation. *J Clin Psychopharmacol*. 20(3): 325-327.
98. Waller, P. 2003. Dealing with uncertainty in drug safety: lessons for the future from sertindole. *Pharmacoepidemiol Drug Saf*. 12(4): 283-287; discussion 289-290.
99. Zimbroff, D.L., Kane, J.M., Tamminga, C.A., Daniel, D.G., Mack, R.J., *et al.* 1997. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. Sertindole Study Group. *Am J Psychiatry*. 154(6): 782-791.

100. van Kammen, D.P., McEvoy, J.P., Targum, S.D., Kardatzke, D. and Sebree, T.B. 1996. A randomized, controlled, dose-ranging trial of sertindole in patients with schizophrenia. *Psychopharmacology (Berl)*. 124(1-2): 168-175.
101. Rampe, D., Murawsky, M.K., Grau, J. and Lewis, E.W. 1998. The antipsychotic agent sertindole is a high affinity antagonist of the human cardiac potassium channel HERG. *J Pharmacol Exp Ther*. 286(2): 788-793.
102. Luisi, A.F. 2002. Aripiprazole: First of a new class of antipsychotics. *Formulary*. 37(11): 575-582.
103. Potkin, S.G., Saha, A.R., Kujawa, M.J., Carson, W.H., Ali, M., *et al*. 2003. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry*. 60(7): 681-690.
104. Kane, J.M., Carson, W.H., Saha, A.R., McQuade, R.D., Ingenito, G.G., *et al*. 2002. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry*. 63(9): 763-771.
105. Keck, P.E.J. and McElroy, S.L. 2003. Aripiprazole, a partial dopamine D2 receptor agonist antipsychotic. *Expert Opinion on Investigational Drugs*. 12(4): 655-662.
106. Kowatch, R.A. and DelBello, M.P. 2003. The use of mood stabilizers and atypical antipsychotics in children and adolescents with bipolar disorders. *CNS Spectrums*. 8(4): 273-280.
107. Reilly, J.G., Ayis, S.A., Ferrier, I.N., Jones, S.J. and Thomas, S.H. 2002. Thioridazine and sudden unexplained death in psychiatric in-patients. *Br J Psychiatry*. 180: 515-522.
108. Kelly, H.G., Fay, J.E. and Lavery, S.G. 1963. Thioridazine hydrochloride (Mellaril): its effect on the electrocardiogram and a report of two fatalities with electrocardiographic abnormalities. *Can Med Assoc J*. 89: 546-554.
109. Glassman, A.H. and Bigger, J.T., Jr. 2001. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry*. 158(11): 1774-1782.
110. Liberatore, M.A. and Robinson, D.S. 1984. Torsade de pointes: a mechanism for sudden death associated with neuroleptic drug therapy? *J Clin Psychopharmacol*. 4(3): 143-146.

111. Reilly, J.G., Ayis, S.A., Ferrier, I.N., Jones, S.J. and Thomas, S.H. 2000. QTc-interval abnormalities and psychotropic drug therapy in patients. *Lancet*. 355(9209): 1048-1052.
112. Hulisz, D.T., Dasa, S.L., Black, L.D. and Heiselman, D.E. 1994. Complete heart block and torsade de pointes associated with poisoning. *Pharmacotherapy*. 14(2): 239-245.
113. Mehtonen, O.P., Aranko, K., Malkonen, L. and Vapaatalo, H. 1991. A survey of sudden death associated with the use of antipsychotic or antidepressant drugs: 49 cases in Finland. *Acta Psychiatr Scand*. 84(1): 58-64.
114. Buckley, N.A., Whyte, I.M. and Dawson, A.H. 1995. Cardiotoxicity more common in thioridazine overdose than with other neuroleptics. *J Toxicol Clin Toxicol*. 33(3): 199-204.
115. Anonymous. Novartis Pharmaceuticals. 2000. Important Drug Warning, Mellaril (thioridazine). <http://www.fda.gov/medwatch/safety/2000/mellar.htm>. (Accessed September 4, 2003)
116. Hartigan-Go, K., Bateman, D.N., Nyberg, G., Martensson, E. and Thomas, S.H. 1996. Concentration-related pharmacodynamic effects of thioridazine and its metabolites in humans. *Clin Pharmacol Ther*. 60(5): 543-553.
117. Schmidt, W. and Lang, K. 1997. Life-threatening dysrhythmias in severe thioridazine poisoning treated with physostigmine and transient atrial pacing. *Crit Care Med*. 25(11): 1925-1930.
118. Czekalla, J., Kollack-Walker, S. and Beasley, C.M., Jr. 2001. Cardiac safety parameters of olanzapine: comparison with other and typical antipsychotics. *J Clin Psychiatry*. 62(Suppl 2): 35-40.
119. Le Blaye, I., Donatini, B., Hall, M. and Krupp, P. 1993. Acute overdosage with thioridazine: a review of the available clinical exposure. *Vet Hum Toxicol*. 35(2): 147-150.
120. Anonymous. Consumer Law News. 2001. Black Box Warning Required for Serzone. <http://www.consumerjusticegroup.com/serzone.htm>. (Accessed March 5, 2004)
121. Findling, R.L., McNamara, N.K. and Gracious, B.L. 2003. *Antipsychotic agents: traditional and atypical*. In *Pediatric Psychopharmacology*. A. Martin, L. Scahill, D.S. Charney, and J.F. Leckman, editors. New York: Oxford University Press. 791.

122. Sachdev, P. 2001. The prolongation of QTc-interval by thioridazine. *Aust N Z J Psychiatry*. 35(6): 857-858.
123. Ray, W.A. and Meador, K.G. 2002. Antipsychotics and sudden death: is thioridazine the only bad actor? *Br J Psychiatry*. 180: 483-484.
124. Hoehns, J.D., Stanford, R.H., Geraets, D.R., Skelly, K.S., Lee, H.C., *et al.* 2001. Torsades de pointes associated with chlorpromazine: case report and review of associated ventricular arrhythmias. *Pharmacotherapy*. 21(7): 871-883.
125. Thomas, D., Wu, K., Kathofer, S., Katus, H.A., Schoels, W., *et al.* 2003. The antipsychotic drug chlorpromazine inhibits HERG potassium. *Br J Pharmacol*. 139(3): 567-574.
126. Ochiai, H., Kashiwagi, M., Usui, T., Oyama, Y., Tokita, Y., *et al.* 1990. [Torsade de Pointes with T wave alternans in a patient receiving dose of chlorpromazine: report of a case]. *Kokyu To Junkan*. 38(8): 819-822.
127. Hameer, O., Collin, K., Ensom, M.H. and Lomax, S. 2001. Evaluation of droperidol in the acutely agitated child or adolescent. *Can J Psychiatry*. 46(9): 864-865.
128. Joshi, P.T., Hamel, L., Joshi, A.R. and Capozzoli, J.A. 1998. Use of droperidol in hospitalized children. *J Am Acad Child Adolesc Psychiatry*. 37(2): 228-230.
129. Fraser, J.A. 2003. *Agitation and aggression*. In *Pediatric Psychopharmacology*. A. Martin, L. Scahill, D.S. Charney, and J.F. Leckman, editors. New York: Oxford University Press.
130. Anonymous. Akorn Pharmaceuticals. 2001. Important Drug Warning, Inapsine (droperidol). <http://www.fda.gov/medwatch/safety/2001/inapsine.htm>. (Accessed September 4, 2003)
131. Woollorton, E. 2002. Droperidol: cardiovascular toxicity and deaths. *Can Med Assoc J*. 166(7): 932.
132. Lischke, V., Behne, M., Doelken, P., Schledt, U., Probst, S., *et al.* 1994. Droperidol causes a dose-dependent prolongation of the QT interval. *Anesth Analg*. 79(5): 983-986.
133. Lawrence, K.R. and Nasraway, S.A. 1997. Conduction disturbances associated with administration of antipsychotics in the critically ill: a review of the literature. *Pharmacotherapy*. 17(3): 531-537.

134. Shale, J.H., Shale, C.M. and Mastin, W.D. 2003. A review of the safety and efficacy of droperidol for the rapid of severely agitated and violent patients. *J Clin Psychiatry*. 64(5): 500-505.
135. Jackson, T., Ditmanson, L. and Phibbs, B. 1997. Torsade de pointes and low-dose oral haloperidol. *Arch Intern Med*. 157(17): 2013-2015.
136. O'Brien, J.M., Rockwood, R.P. and Suh, K.I. 1999. Haloperidol-induced torsade de pointes. *Ann Pharmacother*. 33(10): 1046-1050.
137. Su, K.P., Shen, W.W., Chuang, C.L., Chen, K.P. and Chen, C.C. 2003. A pilot cross-over design study on QTc interval prolongation with sulpiride and haloperidol. *Schizophr Res*. 59(1): 93-94.
138. Fulop, G., Phillips, R.A., Shapiro, A.K., Gomes, J.A., Shapiro, E., *et al*. 1987. ECG changes during haloperidol and pimozide treatment of Tourette's disorder. *Am J Psychiatry*. 144(5): 673-675.
139. Metzger, E. and Friedman, R. 1993. Prolongation of the corrected QT and torsades de pointes cardiac arrhythmia associated with intravenous haloperidol in the medically. *J Clin Psychopharmacol*. 13(2): 128-132.
140. Yoshida, I., Sakaguchi, Y., Matsuishi, T., Yano, E., Yamashita, Y., *et al*. 1993. Acute accidental overdosage of haloperidol in children. *Acta Paediatr*. 82(10): 877-880.
141. Scialli, J.V. and Thornton, W.E. 1978. Toxic reactions from a haloperidol overdose in two children. Thermal cardiac manifestations. *J Am Med Assoc*. 239(1): 48-49.
142. Anonymous. 1985. *The Medical Letter*. 27(678): 2-3.
143. Flockhart, D.A., Drici, M.D., Kerbusch, T., Soukhova, N., Richard, E., *et al*. 2000. Studies on the mechanism of a fatal clarithromycin-pimozide interaction in a patient with Tourette syndrome. *J Clin Psychopharmacol*. 20(3): 317-324.
144. Shapiro, E., Shapiro, A.K., Fulop, G., Hubbard, M., Mandeli, J., *et al*. 1989. Controlled study of haloperidol, pimozide and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry*. 46(8): 722-730.
145. Kang, J., Wang, L., Cai, F. and Rampe, D. 2000. High affinity blockade of the HERG cardiac K(+) channel by the neuroleptic pimozide. *Eur J Pharmacol*. 392(3): 137-140.
146. Thomas, S.H. 1994. Drugs, QT interval abnormalities and ventricular arrhythmias. *Adverse Drug React Toxicol Rev*. 13(2): 77-102.

147. Fayek, M., Kingsbury, S.J., Zada, J. and Simpson, G.M. 2001. Cardiac effects of antipsychotic medications. *Psychiatr Serv.* 52(5): 607-609.
148. Anonymous. 1999. ORAP (pimozide) Tablets. www.pdr.net. (Accessed September 6, 2003)
149. King, R.A. 2003. *Tourette's syndrome and other tic disorders*. In *Pediatric Psychopharmacology*. A. Martin, L. Scahill, D.S. Charney, and J.F. Leckman, editors. New York: Oxford University Press.
150. Krahenbuhl, S., Sauter, B., Kupferschmidt, H., Krause, M., Wyss, P.A., *et al.* 1995. Case report: reversible QT prolongation with torsades de pointes in a patient with pimozide intoxication. *Am J Med Sci.* 309(6): 315-316.
151. Ernst, M., Magee, H.J., Gonzalez, N.M., Locascio, J.J., Rosenberg, C.R., *et al.* 1992. Pimozide in autistic children. *Psychopharmacol Bull.* 28(2): 187-191.
152. Newcorn, J.H., Schulz, K., Harrison, M., DeBellis, M.D., Udarbe, J.K., *et al.* 1998. Alpha 2 adrenergic agonists. Neurochemistry, efficacy, and clinical guidelines for use in children. *Pediatr Clin North Am.* 45(5): 1099-1022, viii.
153. Scahill, L., Chappell, P.B., Kim, Y.S., Schultz, R.T., Katsoyich, L., *et al.* 2001. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *Am J Psychiatry.* 158(7): 1067-1074.
154. MacDonald, E., Kobilka, B.K. and Scheinin, M. 1997. Gene targeting--homing in on alpha 2-adrenoceptor-subtype function. *Trends Pharmacol Sci.* 18(6): 211-219.
155. Williams, P.L., Krafcik, J.M., Potter, B.B., Hooper, J.H. and Hearne, M.J. 1977. Cardiac toxicity of clonidine. *Chest.* 72(6): 784-785.
156. Chandran, K.S. 1994. ECG and clonidine. *J Am Acad Child Adolesc Psychiatry.* 33(9): 1351-1352.
157. Dawson, P.M., Vander Zanden, J.A., Werkman, S.L., Washington, R.L. and Tyma, T.A. 1989. Cardiac dysrhythmia with the use of clonidine in explosive disorder. *DICP.* 23(6): 465-466.
158. Blackman, J.A., Samson-Fang, L. and Gutgesell, H. 1996. Clonidine and electrocardiograms. *Pediatrics.* 98(6 Pt 1): 1223-1224.
159. Kofoed, L., Tadeballi, G., Oesterheld, J.R., Awadallah, S. and Shapiro, R. 1999. Case series: clonidine has no systematic effects on PR or QTc children. *J Am Acad Child Adolesc Psychiatry.* 38(9): 1193-1196.

160. Anderson, R.J., Hart, G.R., Crumpler, C.P. and Lerman, M.J. 1981. Clonidine overdose: report of six cases and review of the literature. *Ann Emerg Med.* 10(2): 107-112.
161. Maggi, J.C., Iskra, M.K. and Nussbaum, E. 1986. Severe clonidine overdose in children requiring critical care. *Clin Pediatr (Phila).* 25(9): 453-455.
162. Mathew, P.M., Addy, D.P. and Wright, N. 1981. Clonidine overdose in children. *Clin Toxicol.* 18(2): 169-173.
163. Van Dyke, M.W., Bonace, A.L. and Ellenhorn, M.J. 1990. Guanfacine overdose in a pediatric patient. *Vet Hum Toxicol.* 32(1): 46-47.
164. Peters, R.W., Hamilton, B.P., Hamilton, J., Kuzbida, G. and Pavlis, R. 1983. Cardiac arrhythmias after abrupt clonidine withdrawal. *Clin Pharmacol Ther.* 34(4): 435-439.
165. Wilens, T.E., Spencer, T.J., Swanson, J.M., Connor, D.F. and Cantwell, D. 1999. Combining methylphenidate and clonidine: a clinically sound medication option. *J Am Acad Child Adolesc Psychiatry.* 38(5): 614-619; discussion 619-622.
166. Maloney, M.J. and Schwam, J.S. 1995. Clonidine and sudden death. *Pediatrics.* 96(6): 1176-1177.
167. Gutgesell, H., Atkins, D., Barst, R., Buck, M., Franklin, W., *et al.* 1999. AHA scientific statement: cardiovascular monitoring of children and adolescents receiving psychotropic drugs. *J Am Acad Child Adolesc Psychiatry.* 38(8): 1047-1050.
168. Kerr, G.W., McGuffie, A.C. and Wilkie, S. 2001. Tricyclic antidepressant overdose: a review. *Emerg Med J.* 18(4): 236-241.
169. Wilens, T.E., Biederman, J., Baldessarini, R.J., Geller, B., Schleifer, D., *et al.* 1996. Cardiovascular effects of therapeutic doses of tricyclic antidepressants in children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 35(11): 1491-1501.
170. Walsh, B.T., Greenhill, L.L., Giardina, E.G., Bigger, J.T., Waslick, B.D., *et al.* 1999. Effects of desipramine on autonomic input to the heart. *J Am Acad Child Adolesc Psychiatry.* 38(9): 1186-1192.
171. Waslick, B.D., Walsh, B.T., Greenhill, L.L., Giardina, E.G., Sloan, R.P., *et al.* 1999. Cardiovascular effects of desipramine in children and adults during exercise testing. *J Am Acad Child Adolesc Psychiatry.* 38(2): 179-186.

172. Fletcher, S.E., Case, C.L., Sallee, F.R., Hand, L.D. and Gillette, P.C. 1993. Prospective study of the electrocardiographic effects of imipramine in children. *J Pediatr*. 122(4): 652-654.
173. Alter, P., Tontsch, D. and Grimm, W. 2001. Doxepin-induced torsade de pointes tachycardia. *Ann Intern Med*. 135(5): 384-385.
174. Casazza, F., Fiorista, F., Rustici, A. and Brambilla, G. 1986. [Torsade de pointes caused by tricyclic antidepressive agents. Description of a clinical case]. *G Ital Cardiol*. 16(12): 1058-1061.
175. Jerjes Sanchez Diaz, C., Garcia Hernandez, N., Gonzalez Carmona, V.M. and Rosado Buzzo, A. 1985. [Helicoidal ventricular tachycardia caused by amitriptyline. of a case]. *Arch Inst Cardiol Mex*. 55(4): 353-356.
176. Davison, E.T. 1985. Amitriptyline-induced Torsade de Pointes. Successful therapy with pacing. *J Electrocardiol*. 18(3): 299-301.
177. Strasberg, B., Coelho, A., Welch, W., Swiryn, S., Bauernfeind, R., *et al*. 1982. Doxepin induced torsade de pointes. *Pacing Clin Electrophysiol*. 5(6): 873-877.
178. Federici, L., Bravi, A., Cesareo, B., Buscalferri, A. and Giangregorio, N. 1987. [Recurrent ventricular tachycardia, torsade de pointes type, in a under chronic treatment with tricyclic drugs. Clinical and therapeutic considerations]. *Minerva Anesthesiol*. 53(3): 107-110.
179. Watson, A. 1998. Tricyclic antidepressants and sudden death. *J Am Acad Child Adolesc Psychiatry*. 37(7): 683-684.
180. Werry, J.S., Biederman, J., Thisted, R., Greenhill, L. and Ryan, N. 1995. Resolved: cardiac arrhythmias make desipramine an unacceptable choice in children. *J Am Acad Child Adolesc Psychiatry*. 34(9): 1239-1245; discussion 1245-1238.
181. Biederman, J., Thisted, R.A., Greenhill, L.L. and Ryan, N.D. 1995. Estimation of the association between desipramine and the risk for sudden death in 5- to 14-year-old children. *J Clin Psychiatry*. 56(3): 87-93.
182. Gunderson, K. and Geller, B. 2003. *Antidepressants II: tricyclic agents*. In *Pediatric Psychopharmacology*. A. Martin, L. Scahill, D.S. Charney, and J.F. Leckman, editors. New York: Oxford University Press. 791.
183. Glassman, A.H. and Preud'homme, X.A. 1993. Review of the cardiovascular effects of heterocyclic antidepressants. *J Clin Psychiatry*. 54(Suppl): 16-22.

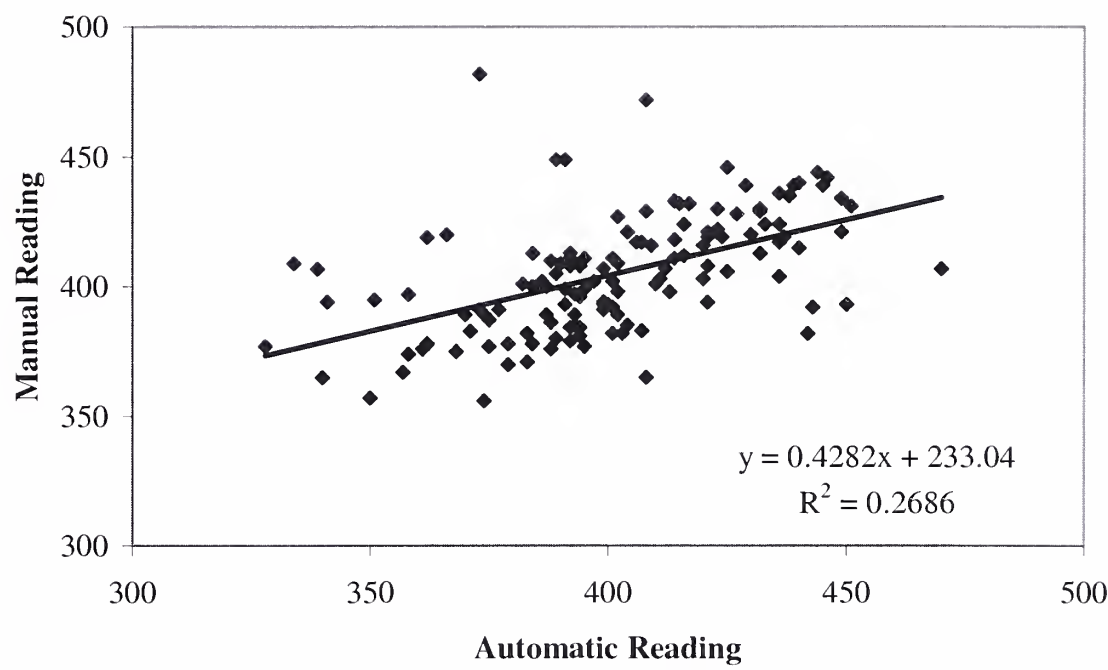
184. Biggs, J.T., Spiker, D.G., Petit, J.M. and Ziegler, V.E. 1977. Tricyclic antidepressant overdose: incidence of symptoms. *J Am Med Assoc.* 238(2): 135-138.
185. James, L.P. and Kearns, G.L. 1995. Cyclic antidepressant toxicity in children and adolescents. *J Clin Pharmacol.* 35(4): 343-350.
186. Boehnert, M.T. and Lovejoy, F.H., Jr. 1985. Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of antidepressants. *N Engl J Med.* 313(8): 474-479.
187. Francis, P.D. 2002. Effects of psychotropic medications on the pediatric electrocardiogram and recommendations for monitoring. *Current Opinion in Pediatrics.* 14: 224-230.
188. Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., *et al.* 1997. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data [see comments]. *J Am Acad Child Adolesc Psychiatry.* 36(7): 980-988.
189. Lord, C., Rutter, M. and Le Couteur, A. 1994. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord.* 24(5): 659-685.
190. Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., *et al.* 1989. Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *J Autism Dev Disord.* 19(2): 185-212.
191. Lord, C., Risi, S., Lambrecht, L., Cook, E.H., Jr., Leventhal, B.L., *et al.* 2000. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord.* 30(3): 205-223.
192. Guy, W. 1976. Clinical Global Impression (CGI). In: *ECDEU Assessment Manual for Psychopharmacology (publication no. 76-338)*. Washington, DC: US Department of Health, Education and Welfare.
193. Leckman, J.F., Riddle, M.A., Hardin, M.T., Ort, S.I., Swartz, K.L., *et al.* 1989. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry.* 28(4): 566-573.
194. Scahill, L., Riddle, M.A., McSwiggin-Hardin, M., Ort, S.I., King, R.A., *et al.* 1997. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. *J Am Acad Child Adolesc Psychiatry.* 36(6): 844-852.

195. Aman, M.G., Singh, N.N., Stewart, A.W. and Field, C.J. 1985. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. *Am J Ment Defic.* 89(5): 485-491.
196. Aman, M.G., Singh, N.N., Stewart, A.W. and Field, C.J. 1985. Psychometric characteristics of the aberrant behavior checklist. *Am J Ment Defic.* 89(5): 492-502.
197. Aman, M.G., Richmond, G., Stewart, A.W., Bell, J.C. and Kissel, R.C. 1987. The aberrant behavior checklist: factor structure and the effect of subject variables in American and New Zealand facilities. *Am J Ment Defic.* 91(6): 570-578.
198. Wechsler, D. 1992. Manual for the Wechsler Intelligence Scale for Children (3rd edition). *San Antonio, Texas: The Psychological Corporation.*
199. Leiter, R.G. 1948. Leiter International Performance Scale. *Chicago, Illinois: Stoelting.*
200. Vineland Adaptive Behavior Scales (Expanded Edition) Sparrow, S., Balla, D. and Cicchetti, D. 1984. *Vineland Adaptive Behavior Scales (Expanded Edition).* American Guidance Service: Circle Pines, MN pp.
201. Jekel, J.F., Elmore, J.G. and Katz, D.L. 1996. *Epidemiology, Biostatistics, and Preventive Medicine.* Saunders Text and Review Series. Philadelphia: W. B. Saunders Company. 297 pp.
202. Newcorn, J.H., Schulz, K.P. and Halperin, J.M. 2003. *Adrenergic agonists: clonidine and guanfacine.* In *Pediatric Psychopharmacology.* A. Martin, L. Scahill, D.S. Charney, and J.F. Leckman, editors. New York: Oxford University Press. 791.
203. Hunt, R.D., Capper, L. and O'Connell, P. 1990. Clonidine in child and adolescent psychiatry. *J Child Adolesc Psychopharmacol.* 1: 87-102.
204. Oesterheld, J. and Tervo, R. 1996. Clonidine: a practical guide for usage in children. *S D J Med.* 49(7): 234-237.
205. Nagy, D., DeMeersman, R., Gallagher, D., Pietrobelli, A., Zion, A.S., *et al.* 1997. QTc interval (cardiac repolarization): lengthening after meals. *Obes Res.* 5(6): 531-537.
206. Shapiro, A.K., Shapiro, E. and Fulop, G. 1987. Pimozide treatment of tic and Tourette disorders. *Pediatrics.* 79(6): 1032-1039.

207. Dulcan, M.K. and Benson, R.S. 1997. AACAP Official Action. Summary of the practice parameters for the assessment and treatment of children, adolescents, and adults with ADHD. *J Am Acad Child Adolesc Psychiatry*. 36(9): 1311-1317.
208. Gundersen, K. and Geller, B. 2003. *Antidepressants II: tricyclic agents*. In *Pediatric Psychopharmacology*. A. Martin, L. Scahill, D.S. Charney, and J.F. Leckman, editors. New York: Oxford University Press. 791.
209. Anonymous. Indiana University/Purdue University at Indianapolis. 2003. Drug Interactions: Cytochrome P450 System. <http://medicine.iupui.edu/flockhart/>. (Accessed October, 2003)
210. Anonymous. Arizona Center for Education and Research on Therapeutics. 2003. Drugs that Prolong the QT Interval and/or Induce Torsades de Pointes Ventricular Arrhythmia. <http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm>. (Accessed October, 2003)

FIGURE 1

QTc interval measurement by two methods (milliseconds)



Number of electrocardiograms = 134

TABLE 1

Overview of electrocardiographic monitoring in pediatric psychopharmacology

1. If considering one of these drugs, schedule a screening visit.
 - a. For TCAs: Reserve as second- or third-line therapy.
2. Screening visit: Complete history and physical (13, 167, 202).
 - a. History
 - i. Symptoms: syncope (202), near-syncope, palpitations (187)? If yes, consider referral to pediatric cardiologist for workup of possible congenital LQTS (167).
 - ii. Heart problems? If yes, do not prescribe clonidine (202); consider consult with pediatric cardiologist if considering other meds.
 - iii. Renal disease? If yes, do not prescribe clonidine (202).
 - iv. Is the child taking any other medications? Consider potentially dangerous interactions (see **Table 3** for examples) (167, 187).
 - v. For antipsychotics especially: Inquire about cardiac risk factors.
 - b. Family history: Consider consult with pediatric cardiologist if positive for:
 - i. Heart disease, sudden/unexplained death, LQTS, deafness, tachydysrhythmias, seizures, syncope (167, 187, 202).
 - ii. For TCAs especially: AV block, IV conduction delay, Wolff-Parkinson-White syndrome or other conduction problems, structural problems, rhythm disturbances.
 - c. Physical exam

- i. Measure vital signs. If pulse < 60 or BP > 2 standard deviations above age norms, consider consult with pediatric cardiologist (167, 203, 204).
- ii. Heart murmurs? If not innocent, refer to pediatric cardiologist (202).
- iii. For antipsychotics especially: Measure weight.
- iv. ECG general guidelines: Obtain before breakfast to avoid midafternoon T-wave changes (38, 147). In adults at least the QTc is longer after a meal (205); avoid postprandial ECGs. Attempt to obtain at physiologic heart rates to avoid inaccuracy in Bazett correction. For TCAs, phenothiazine antipsychotics, and pimozide especially: obtain baseline ECG (167). Parameters should include PR less than or equal to 200 msec and QRS duration less than or equal to 120 msec (187). Choose alternate therapy, if possible, if QTc >450 msec. Avoid pimozide if QTc >440 msec (144, 206). Consider obtaining ECG before prescribing clonidine; not all authorities agree (167, 207). Kowatch and DelBello (106) recommend a baseline ECG before starting ziprasidone, as does this author.
- d. Laboratory data
 - i. For clonidine: CBC/diff, lytes/BUN/Cr/fasting glucose, TFTs, LFTs (203), also K, Mg (4).
 - ii. For antipsychotics: Electrolytes/BUN/Cr/fasting glucose, LFTs, lipids, Ca, Mg (147).
- e. Educate family about proposed drug's risks and benefits, as well as signs and symptoms of possible adverse reactions, and about the need to avoid P450 interactions with other drugs.

3. If all is well, begin drug at lowest possible therapeutic dose (13). Consider drug interactions: for example, with alpha agonists, avoid beta-blockers (165). Also, stop them before stopping clonidine (202), and use TCAs and CNS depressants with caution.

4. Follow-up visits:

a. History

i. Symptoms: Syncope, near-syncope, palpitations? For alpha-agonists especially: dizziness, fatigue, lightheadedness, sedation. If yes, especially with exercise, consider referral to pediatric cardiologist for Holter monitoring and echocardiography (204). Also for alpha agonists: Ask about withdrawal symptoms, such as tachycardia and tachypnea. Ask about fatigue, bradycardia, diminished blood pressure. If present, decrease dose.

ii. Other medications? If so, consider possible interactions (167). For TCAs, obtain blood levels.

b. Physical

i. Measure vital signs, including orthostatic set. Refer to pediatric cardiologist and consider alternate therapy if $HR > 130$. For alpha agonists, if orthostatic change in pulse or increase in BP of greater than 10%, exercise caution with dose increases (202).

ii. For antipsychotics, in case of dose change, addition of new drug, or attainment of steady-state (167, 187), get plasma levels and ECG. QTc should be less than 450 msec. Refer to pediatric cardiologist and consider alternate therapy if resting heart rate > 130 , PR > 200 , QRS > 120 (or $> 25\%$ change from baseline value), QTc > 450 (167) or an increase in QTc from baseline of ≥ 60

msec (37). Other ECG abnormalities should prompt lowering of dose and serial monitoring (167). If T-wave inversions, arrhythmias, or U-waves present, discontinue pimozide, then obtain repeat ECG (144, 206).

iii. Consider monitoring K and Mg, especially during diarrheal illness and with ziprasidone; correct as needed (76).

iv. Francis (187) recommends ascertaining hepatic and renal function after changes in dosage.

v. For antipsychotics: Fayek et al (147) recommend repeating baseline labs mentioned above on at least a yearly basis.

TABLE 2

**Summary guidelines for electrocardiographic monitoring in pediatric
psychopharmacology**

1. Baseline ECG to rule out underlying abnormalities.
2. At a minimum, repeat the ECG at
 - a. Projected target dose (e.g., 5 mg/kg/day of imipramine)
 - b. Halfway to projected target dose
 - c. After any clinical suspicion (e.g., patient reports “skipped beats”)
 - d. At steady state, every three months during the first six months of steady-state, and every six months thereafter.
 - e. For clonidine, if bradycardia, impaired AV conduction, or QRS > 120 msec, consider referral to pediatric cardiologist.
3. Monitor ECG in case of overdose.
4. Pay particular attention to:
 - a. Heart rate > 130 bpm
 - b. PR > 200 msec
 - c. QRS > 120 msec (or >25% change from baseline value),
 - d. QTc > 450 msec,
 - e. QTc increase from baseline of ≥ 60 msec.
5. Bear in mind that manual measurements of intervals are more accurate than intervals measured by the ECG machine.

TABLE 3

Examples of potentially dangerous pharmacotherapeutic combinations

Drug	Potential adverse effect
Tricyclics (TCAs)^A (208)	
plus serotonin-selective reuptake inhibitor	TCA toxicity due to increased levels
plus monoamine oxidase inhibitor	Hypertensive crisis, convulsions, hyperpyrexia, coma
plus neuroleptics	TCA toxicity due to increased levels
plus low-potency neuroleptics	Anticholinergic effects
Alpha agonists (202)	
plus beta blocker	Rebound hypertension if beta blocker withdrawn
plus TCA	Changes in sinus node conduction (controversial)
plus CNS depressants or sedatives	Potential of sedative-hypnotic effect
Antipsychotics^B (121)	
Olanzapine, clozapine, or pimozide plus CYP1A2 inhibitor, such as fluvoxamine	Increase in antipsychotic drug levels
Clozapine, haloperidol, pimozide, or ziprasidone plus CYP3A4 inhibitor, such as clarithromycin	Increase in antipsychotic drug levels
<i>Combinations of medications that both prolong the QTc interval should be avoided.^C</i>	

^A For a more detailed and complete list of interactions of TCAs with other medications, see Gundersen and Geller (208).

^B For a detailed website on drugs involved in cytochrome P450 interactions, see page at University of Indiana/Purdue University at Indianapolis (209).

^C For a detailed website on QTc-prolonging medications, see page at Arizona CERT (210).

TABLE 4

Sample dosing schedule

Day	AM dose (mg)	PM dose (mg)
1	0	5
4	5	5
8	5	10
14	10	10
18	10	15
21	15	15
28	20	20

TABLE 5

**Number of ECGs with prolonged QTc intervals (≥ 440 ms)
as determined by two methods**

		Manual measurement		
		Not prolonged	Prolonged	Total
Automated measurement	Not prolonged	117	9	126
	Prolonged	5	3	8
	Total	122	12	134

Note: Percent agreement = $3/(5+9+3) = 3/17 = 18\%$; kappa = 25.

Sensitivity = $3/(3+9) = 25\%$.

Specificity = $117/(5+117) = 95\%$.

TABLE 6**ECG changes between baseline and peak values**

ECG parameter	Baseline		Peak values		Change		% Change		Statistic	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Max	Mean (SD)	Max	t	p
HR (bpm)	78(18)	(50,117)	92(19)	(65,149)	14(11)	38	20(18)	76	5.64	<.001
PR (ms)	133(21)	(100,177)	148(16)	(122,187)	14(14)	50	12(13)	47	4.62	<.001
QRS (ms)	82(9)	(54,103)	82(8)	(54,91)	0(7)	10	1(7)	12	0.17	0.87
QTc (ms)	402(29)	(328,449)	430(21)	(397,470)	28(26)	114	7(8)	35	4.71	<0.01

Note: ECG, electrocardiogram; SD, standard deviation; HR, heart rate; bpm, beats per minute; ms, milliseconds; Max, maximum; QTc, corrected QT (Bazett method).

Number of subjects = 20.

Number of manually-measured electrocardiograms = 176.

TABLE 7

QTc values over time of subjects with values ≥ 440 msec
(manual measurement)

Time	Subject identification number, age (yr), sex							
	#35 13, M	#37 13, M	#38 9, M	#41 13, F	#43 16, M	#47 19, F	#48 17, M	#49 16, M
Screening	328	432	384	436	391	421/445 ^A	430	436
Day 7	362	422	419	421	450	437	401	438
Day 14	334	470	408	414	399	429	394	444
Day 21	358	366	414	393	420	446		423
Day 28	350	367	443	425		449	436	405
Day 42				432				
Day 56	388	448		427		435	420	416
Month 3	379	428		451		440	339	423
Month 4	442	362		453		440	406	
Month 5	373	402		440		417	400	415
Month 6	387	414		400		439	446	440
^A Patient received two pre-medication EKGs.								

Note: M, male; F, female.

Some patients received fewer EKGs owing to trial discontinuation.

Values ≥ 450 msec are bolded.

TABLE 8**Patients experiencing discrete increases over baseline:****Manufacturer vs. current study**

QTc increase over baseline (msec)	Number of subjects (%)		p
	Manufacturer (77) (n = 33)	Current study (n = 20)	
≥ 30	21 (64)	8 (40)	0.082
≥ 60	7 (21)	1 (5)	0.112
≥ 75	1 (3)	1 (5)	0.617

Note: Patients with greater changes were also counted in groups of lesser change.

When patients received two pre-medication EKGs in our study, the lower baseline QTc was used to calculate changes.

p refers to results of chi-square test (in 30-msec group) or Fisher's exact test (in 60 and 75-msec groups).

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